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May 1976

FINAL REPORT

Office of Toxic Substances
U.S. Environmental Protection Agency
Washington, D.C. 20460

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This report reviews the potential environmental hazard from the commercial use of ketonic solvents with the exception of acetone. Three ketones - cyclohexanone, methyl ethyl ketone, and methyl isobutyl ketone - dominate the market. Other commercial ketonic solvents include diacetone alcohol, isophorone, mesityl oxide, and acetophenone. Information on physical and chemical properties, production methods and quantities, commercial uses and factors affecting environmental contamination, as well as information related to health and biological effects, are reviewed.

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Executive Summary

The environmental hazard potential of the commercially significant ketonic solvents with the exception of acetone is reviewed. Based on 1973 consumption values, the total consumption of these ketones approximates 1.5 billion pounds yearly. Three ketones dominate this market: cyclohexanone (638 million pounds), methyl ethyl ketone (505 million pounds), and methyl isobutyl ketone (155 million pounds). While methyl ethyl ketone and methyl isobutyl ketone are used primarily as solvents, 95% of the cyclohexanone is utilized as a chemical intermediate. The most important of the remaining commercial ketones are diacetone alcohol, isophorone, mesityl oxide, and acetophenone. Compared to these seven ketones, all other ketones are used in only minor amounts.

The ketonic solvents are principally consumed by industry; a relatively small proportion is formulated into consumer products. The industrial coatings industry dominates their consumption. This includes automobile, metal and metal appliances, wood, paper and textile coatings. Most of the remaining uses are also as solvent applications and include rare metal refining, lube oil dewaxing, printing inks, adhesives, degreasing solvents, paint, varnish, rust removers, pesticides, and industrial processing solvents.

The relative importance for sources of the selected ketones in the environment appears to vary for each ketone. The evaporation of solvent from drying of industrial coatings and allied uses (inks and adhesives) is the major commercial source of ketones which are emitted to the environment. Major non-commercial sources include automotive emissions, formation in photochemical smog processes, and production in food and biological processes (including fermentation). With methyl ethyl ketone, solvent loss is probably the major source of environmental contamination. Major sources of contamination for the other ketones is not clear from the available information.

Environmental exposure to ketonic solvents is poorly understood. The available monitoring data are inadequate and do not allow any estimates of daily intake nor do they give any indication of the major route (oral, inhalation, etc.) of exposure. Many of the compounds are present in food and in human urine. The compounds appear to be relatively biodegradable and photochemically reactive and do not appear to have a high bioaccumulation potential.

The primary biological effect of all the ketonic solvents in acute exposures is narcosis. Based on the available data, renal toxicity seems to be the most common feature of chronic exposures. In addition, two of the ketones, methyl n-butyl ketone and 2,5-hexanedione, are neurotoxic in the sense that they produce central and peripheral nervous system damage during chronic exposure. Dose-response relationships suggest that both of these chronic adverse effects have threshold values well above levels of potential environmental exposure. However, the chronic effects of these compounds have not been extensively studied and most of the information is based on exposures of under 180 days. Little information is available on the carcinogenicity, mutagenicity, and teratogenicity of these chemicals. Therefore, while the available information does not suggest a high potential for adverse environmental effects, the lack of information on many important aspects of ketone toxicity precludes a definitive evaluation of potential environmental hazard.

Introduction

This report examines the potential environmental hazards involved in commercial use of ketones which have significant commercial applications as solvents. Acetone is excluded except where it is representative of ketonic solvents or important to their use or production. The selected ketones have two characteristics: (1) they are produced either in quantities above one thousand pounds or valued at more than one thousand dollars annually and (2) they have recognized applications as solvents. For the former characteristic, publications by either the U.S. International Trade Commission (Annual a) or the Stanford Research Institute (Dictionary of Chemical Producers, 1974 and 1975) were used. The determination that a ketone has solvent applications was provided by consulting the Kirk-Othmer Encyclopedia of Chemical Technology or Stanford Research Institute's Chemical Economics Handbook. For a few ketones, final judgment rested on discussion with the producer.

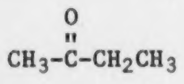
I. Physical and Chemical Data

A. Structure and Properties

1. Chemical Structure

Ketones are organic compounds in which a carbonyl group, C=O, is attached to two carbon atoms. The attached groups can either be equivalent or different, aliphatic and/or aromatic, and the carbonyl group can be contained in a ring structure (alicyclic).

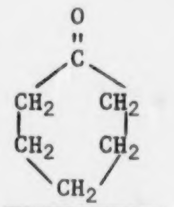
Two commonly used methods of writing structures are shown for methyl ethyl ketone (MEK) and cyclohexanone (CH).



$CH_3-\overset{\overset{O}{\|}}{C}-CH_2CH_3$

$CH_3COCH_2CH_3$

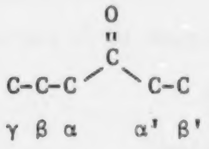
MEK



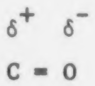
$(CH_2)_5CO$

CH

Table 1 lists the common names, IUPAC system names, and structures used in the text for the ketones selected for study. The IUPAC system names ketones by changing the -e of the parent hydrocarbon to the suffix -one and designating the carbonyl position by number. The chain and other substituents are otherwise numbered by the usual method. The most frequently used common name system describes the groups attached to the carbonyl followed by the word, ketone. Although Cram and Hammond (1959), among other authorities, have suggested that the groups be listed in alphabetical order, many of the common names do not adhere to this suggestion. Thus, methyl ethyl ketone is the commonly recognized name rather than the suggested ethyl methyl ketone. In the common system, functional groups on the chain are designated by Greek letters with the carbon atom adjacent to the carbonyl carbon defined as α. While this system is in general use for the simple aliphatic ketones, the aromatic ketones and diones are often named by other common systems. These generally combine the name of the structurally related carboxylic acids with the ending -one. Examples of this nomenclature are acetophenone (rather than methyl phenyl ketone) and acetylacetone (for 2,4-pentanedione).



The carbonyl group is a polar, unsaturated moiety, in which oxygen is relatively negative.

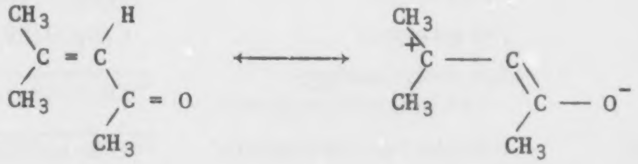


$$\overset{\delta^+}{C} = \overset{\delta^-}{O}$$

Table 1. Nomenclature and Structure of Ketones

Common Name	IUPAC Name	Structure
Acetone	2-Propanone	$(CH_3)_2CO$
Acetylacetone	2,4-Pentanedione	$CH_3COCH_2COCH_3$
Acetonylacetone	2,5-Hexanedione	$CH_3COCH_2CH_2COCH_3$
Acetophenone		$CH_3COC_6H_5$
Benzophenone		$C_6H_5COC_6H_5$
Cyclohexanone	Cyclohexanone	$\overline{(CH_2)_5CO}$
Diacetone alcohol	4-Hydroxy-4-methyl-2-pentanone	$CH_3COCH_2C(OH)(CH_3)_2$
Diethyl ketone	3-Pentanone	$(CH_3CH_2)_2CO$
Diisopropyl ketone	2,4-Dimethyl-3-pentanone	$[(CH_3)_2CH]_2CO$
Isovalerone (Diisobutyl ketone)	2,6-Dimethyl-4-heptanone	$[(CH_3)_2CHCH_2]_2CO$
Ethyl *n*-amyl ketone	3-Octanone	$C_2H_5CO(CH_2)_4CH_3$
Ethyl *n*-butyl ketone	3-Heptanone	$C_2H_5CO(CH_2)_3CH_3$
Isophorone	3,5,5-Trimethyl-cyclohex-2-en-1-one	$\overline{CH_2C(CH_3)_2CH_2COCH{=}C(CH_3)}$
2-Methylcyclohexanone	2-Methylcyclohexanone	$\overline{(CH_2)_4COCH(CH_3)}$
3-Methylcyclohexanone	3-Methylcyclohexanone	$\overline{(CH_2)_3COCH_2CH(CH_3)}$
4-Methylcyclohexanone	4-Methylcyclohexanone	$\overline{CH(CH_3)(CH_2)_2CO(CH_2)_2}$
Methyl ethyl ketone	2-Butanone	$CH_3COC_2H_5$
Methyl isoamyl ketone	5-Methyl-2-hexanone	$CH_3CO(CH_2)_2CH(CH_3)_2$
Methyl isobutyl ketone (Hexone)	4-Methyl-2-pentanone	$CH_3COCH_2CH(CH_3)_2$
Methyl isopropenyl ketone	2-Methyl-1-butene-3-one	$CH_3COC(CH_3){=}CH_2$
Methyl *n*-amyl ketone	2-Heptanone	$CH_3CO(CH_2)_4CH_3$
Methyl *n*-butyl ketone	2-Hexanone	$CH_3CO(CH_2)_3CH_3$
Methyl *n*-hexyl ketone	2-Octanone	$CH_3CO(CH_2)_5CH_3$
Methyl *n*-propyl ketone	2-Pentanone	$CH_3CO(CH_2)_2CH_3$
	4-Methoxy-4-methyl-2-pentanone	$CH_3COCH_2C(OCH_3)(CH_3)_2$
Mesityl oxide	4-Methyl-3-penten-2-one	$CH_3COCH{=}C(CH_3)_2$
Trimethylnonanone (Isobutyl heptyl ketone)	2,6,8-Trimethyl-4-nonanone	$(CH_3)_2CHCH_2COCH_2CH(CH_3)CH_2CH(CH_3)_2$

The simple ketones have dipole moments in the range 2.3 to 2.8D, which represents a 40% to 50% ionic character. The carbonyl oxygen is capable of hydrogen bonding with acidic hydrogens on such compounds as alcohols. The simple ketones do not have sufficiently acidic hydrogen for hydrogen bonding in the pure material. The pi-electrons of the carbonyl group will conjugate with α,β unsaturation on either attached carbon atom and result in the extension of the polar character of the carbonyl function. Unsaturated functional groups, attached at the carbonyl carbon, will orient for maximum conjugation. The conjugation can be depicted as several resonance structures, as shown for mesityl oxide (Roberts and Caserio, 1965).



2. Physical Properties

Physical properties of the ketones are the primary reason for their industrial use as solvents. The most important properties in terms of solvent applications are as follows: (1) vapor pressure, boiling point and rate of evaporation, (2) solvent power and miscibility with other liquids, (3) viscosity and viscosity of solutions, (4) inflammability, flash point, and explosive limit, and (5) toxicity (Taylor and Marks, 1969). All properties except toxicity are examined in this section. Table 2 lists fundamental properties; Table 3 records properties important to the solvent action; and Table 4 contains properties of the ketonic vapors.

Table 2. Physical Properties of Selected Ketones: Basic Properties (From Lurie, 1966; Rowe and Wolfe, 1963; Handbook of Chemistry and Physics, 1972; Union Carbide, 1968; and Browning, 1965)

				Specific Gravity		
Ketone	Molecular weight	Melting Point °C	Boiling Point °C	d_{20}^{20} grams per c.c.	$\frac{\Delta SG}{\Delta t} \times 10^3$ 10 - 40°C	Index of Refraction n_D
Acyclic						
Symmetrical						
Acetone	58.08	-94.6	56.5	0.7917	1.11	1.3591
Diethyl ketone	86.13	-42	101.7	0.8136^{20}_{4}		1.3927
Diisopropyl ketone	114.18		125	0.806^{20}_{4}		1.4170
Diisobutyl ketone	142.24	-41.5	168.4	0.8076	.82	1.4123
Asymmetrical						
Methyl ethyl ketone	72.11	-86.4	79.6	0.8061	1.04	1.3789
Methyl n-propyl ketone	86.11	-77.8	102.3	0.8075	0.98	1.3902
Methyl n-butyl ketone	100.16	-56.9	127.2	0.8300^{20}_{4}		1.4007
Methyl isobutyl ketone	100.16	-84.7	116.2	0.8020	0.94	1.3958
Methyl n-amyl ketone	114.18	-35.5	151.5	0.8166	0.86	1.4007
Methyl isoamyl ketone	114.18		144	0.8132	0.87	
Methyl n-hexyl ketone	128.22	-21.5	173	0.8185^{20}_{4}		1.4152
Ethyl n-butyl ketone	114.18	-36.7	147.8	0.8197	0.98	
Ethyl n-amyl ketone	128.22		169	0.8220		
Trimethylnonanone	184.19		207	0.8598	0.82	1.4273
Mesityl oxide	98.14	-59	129.8	0.8548^{20}_{4}		1.4458
Diacetone alcohol	116.16	-42.8	169.1	0.938	0.91	1.4234
4-Methoxy-4-methyl-2-pentanone	130.	-35.45	160	0.9061	0.90	1.4181
2,4-Pentanedione	100.11	-23	139	0.9721^{20}_{4}		1.4518
2,5-Hexanedione	114.14	-9	194	0.9753	1.02	1.4232
Cyclic						
Cyclohexanone	98.14	-16.4	156	0.9482	0.90	1.4507
2-Methylcyclohexanone	112.17	- 4.0	166	0.9250		1.4505
3-Methylcyclohexanone	112.17		169	0.915		1.4456
4-Methylcyclohexanone	112.17		169	0.912		1.4432
Isophorone	138.20		215.2	0.9255^{20}_{4}	0.78	1.4766
Aromatic						
Acetophenone	120.14	19.55	202.0	1.028^{20}_{4}	0.84	1.536
Benzophenone	182.21	48.1 (α) 26 (β)	305.9	1.146(α) 1.107(β)		1.607(α) 1.606(β)

Table 3. Physical Properties of Selected Ketones: Solvent Properties (From Lurie, 1966; Rowe and Wolfe, 1962; Union Carbide, 1968; Wayart and Dante, 1969; Durrans, 1971; Hansen and Beerbower, 1971)

Ketone	Solubilities Weight percent at 20°C: Ketone in Water	Solubilities Weight percent at 20°C: Water in Ketone	Absolute Viscosity at 20°C in CPS	Volume coefficient of expansion x 10^3 per °C at 20°C	Surface Tension dynes/cm	Solubility Parameter: δ	Solubility Parameter: δ_D	Solubility Parameter: δ_P	Solubility Parameter: δ_H	Molar Volume	Fractional Polarity	Heat of vaporization in BTU/lb.: at 760 mm	Heat of vaporization in BTU/lb.: at 300 mm
Acyclic Symmetrical													
Acetone	complete	complete	0.33	1.43	23.32	10.0	7.6	5.1	3.4	74.0	0.695	219	228
Diethyl ketone	3.4	2.6					7.7	3.7	2.3	106.4			
Diisopropyl ketone	16.6	4.5											
Diisobutyl ketone	0.05	0.75	1.0	0.02	22.5	7.8	7.8	1.8	2.0	177.1	0.123	119	127
Asymmetrical													
Methyl ethyl ketone	26.8	11.8	0.43	1.31	24.6	9.3	7.8	4.4	2.5	90.1	0.510	187	202
Methyl n-propyl ketone	4.3	3.3	0.5	1.2	23.6							167	177
Methyl n-butyl ketone	1.4	2.1											
Methyl isobutyl ketone	2.04	2.41	0.6	1.15	23.64	8.4	7.5	3.0	2.0	125.8	0.315	147	156
Methyl n-amyl ketone	0.43	1.45	0.82	1.04								148	158
Methyl isoamyl ketone	0.54	1.28	0.8	1.07	28.5	8.3	7.8	2.8	2.0	142.8	0.255	142	114
Ethyl n-butyl ketone	0.43	0.78	0.76	1.06	24.6							138	147
Ethyl n-amyl ketone	0.26	0.90		1.25		8.2					0.233		
Mesityl oxide	2.8	3.4	0.6	1.06	22.9	8.2	8.0	3.5	3.0	115.6	0.223	157	166
Diacetone alcohol	complete	complete	3.2	0.94	28.9	9.2					0.312	154	162
2,4-Pentanedione	16.6		0.58		26							152	159
2,5-Hexanedione	3.1												
Cyclic													
Cyclohexanone	2.5		2.2	0.94	27.7	9.9	8.7	3.1	2.5	104.0	0.380	174	184
Isophorone	1.2		2.6	0.85	32.3	9.0	8.1	4.0	3.6	150.5	0.191	135	143
Aromatic													
Acetophenone	0.55						9.6	4.2	1.8	117.4		157	166

Table 4. Physical Properties of Selected Ketones: Vapor Properties (From Rowe and Wolfe, 1963; Wyart and Dante, 1969; Union Carbide, 1968; Durrans, 1971)

Ketone	Vapor Pressure mmHg at 20°C	Δt/ΔF 750-770mm	Percent Ketone in saturated air	Azeotrope with water: Boiling Point °C	Azeotrope with water: Percent Ketone	Flammability range % by Volume: Lower limit	Flammability range % by Volume: Upper limit	Flash Point °F: Tag open cup	Flash Point °F: Tag Closed cup	Auto ignition/ temperature F	Warning Properties[a]: Odor Intensity	Warning Properties[a]: Irritation intensity	Suggested maximum practical working conc. ppm
Acyclic Symmetrical													
Acetone	185.95	0.039	29.8	non-azeotrope		2.15	13.0	15	0		1-2	0-1	1000
Diethyl ketone	-	-	-	-	-	-	-	-	-	1125	-	-	-
Diisopropyl ketone	-	-	-	-	-	-	-	-	-	-	-	-	-
Diisobutyl ketone	1	0.051	2.4	97	48.1			120	30.8	-	4	2	50
Asymmetrical													
Methyl ethyl ketone	70	0.043	13.2	73.4	88	1.8	12.0	20	22	-	2-3	1-2	250
Methyl n-propyl ketone	27	0.044	2.1	83.8	80.4	1.55	8.15	58, 72[c]	45	-	3	1-2	200
Methyl n-butyl ketone	38[b]	-	0.5	-	-	1.22	8.0	-	73	-	3	2	100
Methyl isobutyl ketone	15	0.046	1.0	87.9	76.0	1.35	7.6	74	64	-	3	2	100
Methyl n-amyl ketone	2	0.048	0.21	95.2	54.6	-	-	117	120	-	4	2	75
Methyl isoamyl ketone	4	0.048	0.26	93	25	-	-	120	-	-	3	2	100
Methyl n-hexyl ketone	1.2	-	0.16	-	-	-	-	-	155	1060	3	2	75-100
Ethyl n-butyl ketone	4	0.05	0.18	94.6	57.8	-	-	106	-	-	-	-	-
Ethyl n-amyl ketone	2.0	-	-	-	-	-	-	135	-	-	-	-	-
Trimethylnonanone	<0.5(est.)	-	<0.07(est.)	-	-	-	-	195	-	-	-	-	-
Mesityl oxide	8	0.047	1.25	91.8	68	-	-	84	90	-	2	2	25
Diacetone alcohol	1.2	0.05	0.16	98.8	12.7	-	-	142	-	3840	3	2	50
4-Methoxy-4-methyl-2-pentanone	2.2	-	-	97.6	61.4	-	-	141	-	-	-	-	-
2,4-Pentanedione	7	0.051	-	94.4	59.0	-	-	105	-	-	-	-	-
Cyclic													
Cyclohexanone	2	0.048	0.6	-	-	1.1	-	116	143	1570	1-2	2	100
2-Methylcyclohexanone 3-Methylcyclohexanone 4-Methylcyclohexanone	3	-	0.4	-	-	-	-	-	130	-	1-2	2	100
Isophorone	<1	0.057	0.06	99.5	16.1	0.8	3.8	205	184		2	2	100
Aromatic													
Acetophenone	<1	0.054	-	99.1	18.5			200	180	1102	-	-	-

(a)

Degree	Odor Intensity	Irritation intensity
0	No Odor	No Irritation
1	Very Faint	Faint
2	Faint	Moderate
3	Easily Noticeable	Strong
4	Strong	Intolerable
5	Very Strong	

(b) At 25°C

(c) 58° from Union Carbide, 1968
72° from Wyart and Dante, 1969

The simple, aliphatic ketones are less dense than water; their specific gravities range from 0.79 to 0.86 g/cc, and generally increase with increasing molecular weight. With unsaturation, with additional functional groups or with alicyclic ketones, the specific gravity increases to more than 0.9 g/cc. As the temperature increases, the specific gravity decreases linearly (see Figure 1).

Ketones have higher melting points and boiling points than hydrocarbons and ethers of the corresponding molecular weight and formula, but lower m.p. and b.p. than the corresponding alcohols. They are less flammable than the corresponding ethers. For example, while ethyl ether ($C_4H_{10}O$) boils at 34.5°C and has a flash point (open tag cup) of -34.5°F, methyl ethyl ketone (C_4H_8O) has a boiling point of 79.6°C and a flash point of 24°F (open tag cup) (Durrans, 1971). Figure 2 shows the vapor pressure - temperature relationships of several of the ketones. The ketones possess characteristic odors, the intensities of which increase with increasing molecular weight and unsaturation at the α-carbon.

All of the selected ketones except benzophenone are liquids of similar characteristics at ambient temperature, ca. 25°C. Benzophenone, which exists in two crystalline forms, melts either at 26° (α) or 48° (β). The simple, unsubstituted ketones are neutral; acetylacetone is the most acidic, with K_a of approximately 1.5×10^{-9} (Cram and Hammond, 1959).

Table 5 lists the absorption maxima, molar extinction coefficients, and the assignment of electronic transitions of acetone in cyclohexane. The U.V. spectra of acetone, cyclohexanone, isophorone and 2,5-hexanedione are shown in Figure 3.

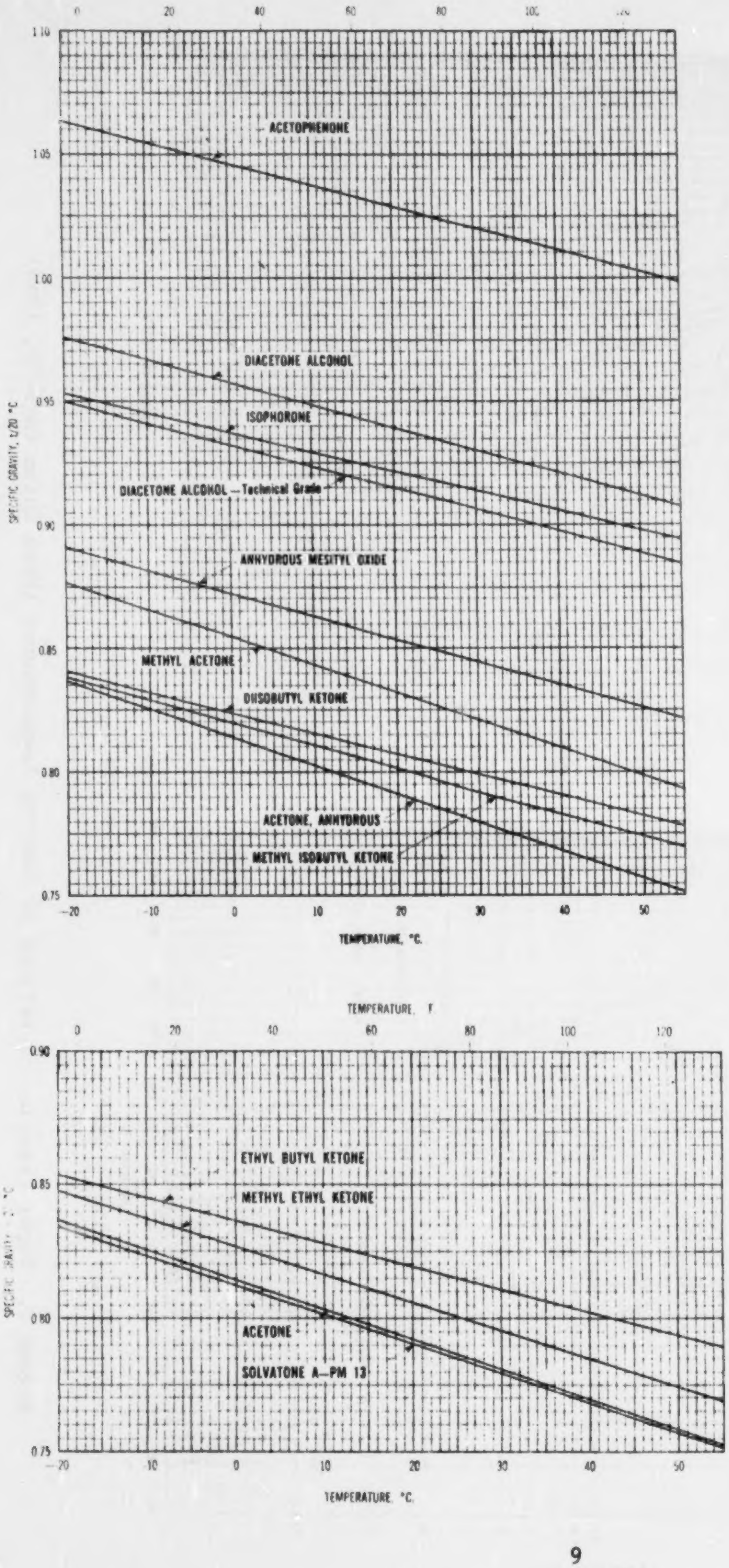


Figure 1. Specific Gravity of Ketones at Various Temperatures (From Union Carbide, 1968)

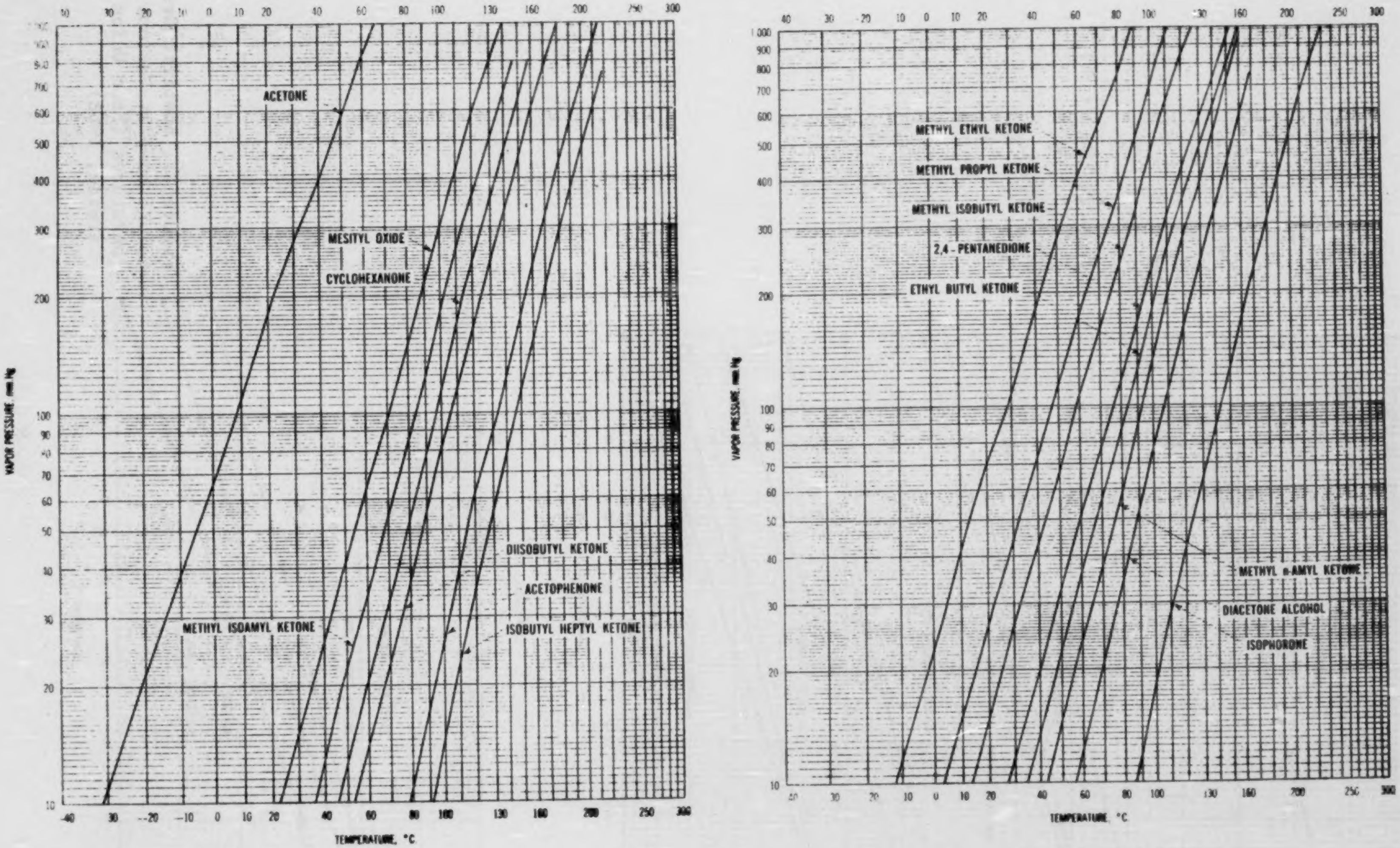
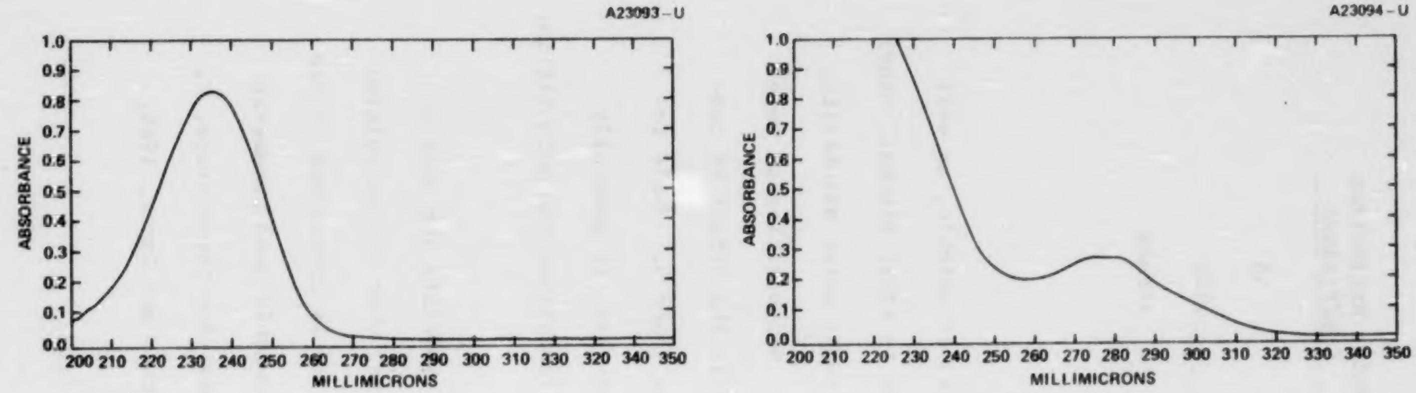
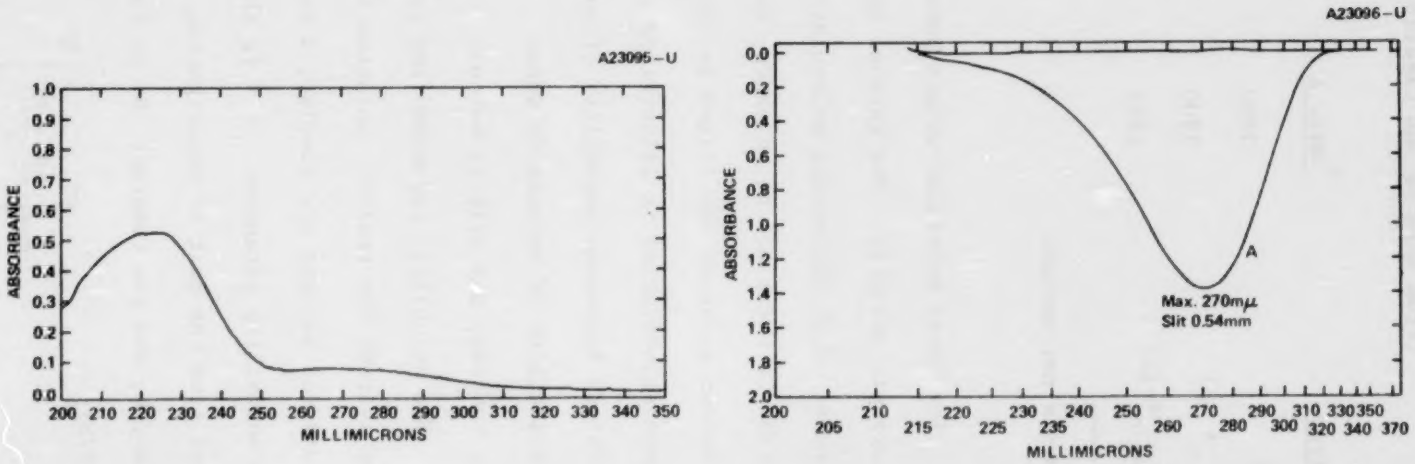


Figure 2. Vapor Pressure of Ketones at Various Temperatures (From Union Carbide, 1968)



1) Acetone
(5.0 g/ℓ in methanol)

2) Cyclohexanone
(0.50 g/ℓ in methanol)



3) Isophorone
(0.0970 g/ℓ in methanol)

4) 2,4-Pentanedione
(0.4496 g/ℓ in methanol)

Figure 3. Ultraviolet Spectra of Acetone (1); Cyclohexanone (2); Isophorone (3); and 2,4-Pentanedione (4) (From Sadtler Index, 1966)

Table 5. Absorbance in the Ultraviolet and Far-Ultraviolet By a Solution of Acetone in Cyclohexane (From Roberts and Caserio, 1965)

Transition Type	$\lambda_{max.}$ A	Molar Extinction Coefficient
$n \longrightarrow \pi^*$	2800	15
$\pi \longrightarrow \pi^*$ (a)	1900	1100
$n \longrightarrow \sigma^*$ (a)	1560	strong

(a) Assignments not certain

The lower molecular weight ketones are water soluble, as well as soluble in organic solvents. The ketones are soluble in ethyl alcohol, ethyl ether, and benzene. With increasing molecular weight, their water solubility, which is important in their use as solvents, decreases. Solubilities of water in ketone and ketone in water are listed in Table 3, while the effect of temperature on these solubilities is illustrated in Figures 4 and 5. While increasing temperature increases solubility of water in ketones, it generally decreases the solubility of ketones in water. Table 6 summarizes the solubilities of some resins, rubbers, and oils in ketones.

The solubility parameter and fractional polarity are used to develop solvent systems for resins. Solution is predicted when the calculated values for solute and solvent are similar; a similar value is considered within one unit. The solubility parameter - δ - is the more commonly used parameter. It is calculated from the heat of vaporization, ΔH, transition temperature, T, molecular volume, V, and gas constant, R, as follows (Wyart and Dante, 1969, and Burrell, 1973):

$$\delta = \left[\frac{\Delta H - RT}{V}\right]^{\frac{1}{2}}$$

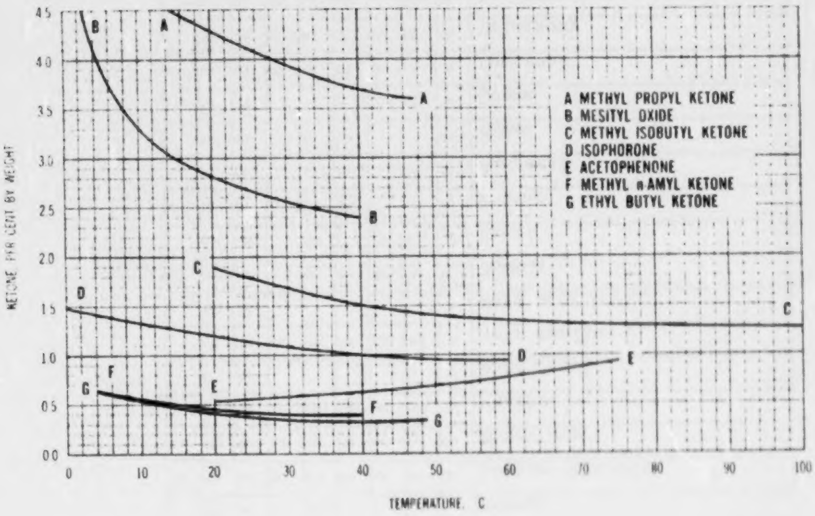


Figure 4. Solubility of Ketones in Water (From Union Carbide, 1968)

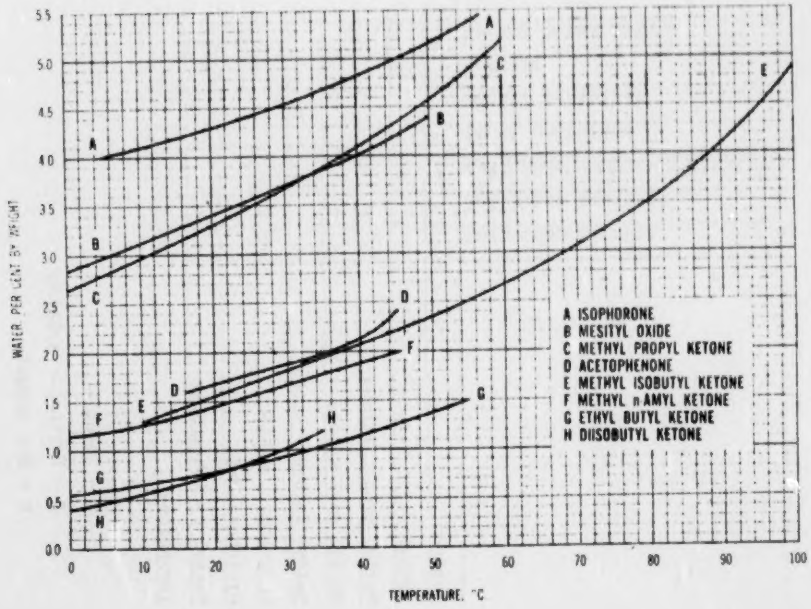


Figure 5. Solubility of Water in Ketones (From Union Carbide, 1968)

Table 6. Solubilities of Resins, Rubbers, and Oils in Ketones (From Durrans, 1971; Drakos *et al*, 1972)

Solvents	Cellulose nitrate	Cellulose acetate	Cellulose acetate butyrate	Ethyl cellulose	Benzyl cellulose	Acrylic	Methyl methacrylate	Alkyd	Epoxy	Polystyrene	Polyvinylacetate	Polyvinylchloride	Polyvinylchloroacetate	Rubber	Rubber chloride	Ester gum	Shellac	Hard copal	Soft manila	Hard manila	Dammar	Kauri	Mastic	Sandarac	Elemi	Congo	Cumarone	Colophony	Paraffin hydrocarbon	Vegetable oil	Castor oil
Acetone	S	S	S	S		S	P	S	S	S	S	P	S		S	S	P	P	S	S	P	P	P	S	S	P	S	S	S	S	S
Methyl ethyl ketone	S		P	S		S		S	S		S				S	S	P		S		P	S		S		S	S	S	S	S	S
Methyl [illegible]opyl ketone	S	N		S							S				S	S	P		S		P	S					S	S			
Methyl amyl ketone	S	N		S							S	S	S		S	S	N		P		P	S	S	S	S		S	S	S	S	S
Methyl isobutyl ketone	S		N	S	S	P		S	S		S	S	S	S	S	S	N		P		S	P	S	S	S		S	S	S	S	S
Di-n-propyl ketone	P	P		S			P				S				S	S			S								S	S	S	S	S
Cyclohexanone	S	S		S	S		S			S	S	S	S	S	S	S	S	S	S	P	P	S	S	S	P	P	S	S	S		
Methyl cyclohexanone	S	S		S	S		S			S	S	S	S	S	S	S	S	S	S	S	P	S	S	S	S	P	S	S	S		
Isophorone	S	S	S	S		P		S	S	S	S	S	S		P												S				

S - Soluble

P - Partially soluble

N - Not soluble

3. Properties of the Commercial Ketones

Table 7 summarizes physical properties of the commercially available ketones. All are marketed as 95% ketone or better. Commercial methylcyclohexanone consists of the three isomers along with some cyclohexanone as impurity: the composition is approximately 45% of the 3-isomer; 35% of the 4-isomer; 2% of the 2-isomer; and 10% of cyclohexanone. The following solvent characteristics of the commercial material are tabulated: evaporation rate, blush resistance, hydrocarbon dilution ratio, viscosity of a cellulose nitrate solution, and weight of ketone per gallon. The dilution ratio measures the extent to which the relatively expensive ketones can be diluted with relatively cheap hydrocarbons. This unitless parameter is defined as the volume ratio of the diluent (hydrocarbon) to solvent (ketone) that just fails to completely dissolve cellulose nitrate (8 g/100 mℓ) in the solvent blend. Blush is caused by cooling due to rapid solvent evaporation, and can be divided into cotton blush, which results from resin precipitation, and moisture blush, which results from condensation of moisture in the film (Martens, 1968; Wyart and Dante, 1969; Union Carbide, 1968).

4. Principal Contaminants in Commercial Products

The principal contaminants specified in the technical grade ketones on the market are:

(1) Acids (acidity)
(2) Water
(3) Alcohols
(4) Non-volatile substances
(5) Suspended matter

Table 7. Physical Properties of the Commercial Ketones (Union Carbide, 1968; Wyart and Dante, 1969; Durrans, 1971)

Ketone	Purity									Evaporation rates		Viscosities cP		Blush	Dilution ratio		
	% Ketone by Weight	% Water by Weight	Acidity % by Weight as Acetic Acid	Alcohol % by Weight	Non-volatiles g/100 ml	Color Pt-Co Units, max.	Odor and Suspended Matter	Specific Gravity d_{20}^{20}	Distillation range, °C @ 760 mm	Relative to n-butyl acetate = 1	Shell Thin Film Evaporometer to 90% evap., sec.	Neat	Cellulose Nitrate solution	Resistance % Relative humidity at 80°F.	Toluene	Aliphatic naptha	Average lbs. per gallon, 20°C
Acetone	99.5	0.5	0.002	-	0.001 max.	5	sharp, penetrating and non-residual	0.7905 - 0.7930	10 including 56.1	6.0	75	0.34	10	<20	4.4	0.8a	6.59
Diethyl ketone	-	-	-	-	-	-	-	0.807 - 0.811	97 - 106	2.5	179	0.47	20	76	3.0	0.7	-
Diisobutyl ketone	95	0.20	0.02	2.0 max. as diisobutyl carbinol	-	20	mild	0.806 - 0.809	163 - 173	0.2	2,470	0.95	126	95	1.5	0.8	6.75
Methyl ethyl ketone	99.5 min.	0.1	0.03	-	0.002 max.	10	non-residual	0.805 - 0.807	1.5 including 79.6±0.1	4.0	112	0.41	15	36	4.3	0.9	6.71
Methyl n-propyl ketone	95.0 min.	19[a]	0.02	-	-	15	no odor requirement	0.805 - 0.810	97.0 - 106.0	1.6	185	0.5	20	70	4.0	1.1	-
Methyl n-butyl ketone	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4.1	-	-
Methyl isobutyl ketone	99.0 min.	0.10	0.01	-	-	15	no odor requirement	0.800 - 0.803	114 - 117°C	1.6	277	0.55	30	78	3.6	1.0	6.67
Methyl n-amyl ketone	95.0 min.	19[a]	0.05	-	0.005 max.	18	mild and non-residual	0.816 - 0.821	147 - 154	0.4	1,250	0.77	42	93	3.9	1.2	-
Methyl isoamyl ketone	98.0 min.	0.1	0.01	-	-	10	characteristic and non-residual	0.813 - 0.817	141 - 148	0.4	1,035	0.73	40	89	3.8	1.1	6.75
Ethyl butyl ketone	97.0 min.	0.3	0.02	-	-	15	mild	0.817 - 0.822	143 - 151	0.5	1,020	0.70	49	94	2.2	0.9	-
Trimethylnonanone	97.5	-	-	-	-	-	-	-	156 - 162	0.2	2,025	0.80	58	96	2.6	0.8	-
Trimethyl nonanone	95.0	0.10	0.01	4.0 max. as trimethylnonanol	-	50	mild	0.820 - 0.825	213 - 223	-	-	-	-	-	-	-	-
Mesityl oxide	97	0.1	0.01	-	-	15	mild and non-residual	0.852 - 0.856	123 - 132	0.8	555	0.62	24	83	4.0	1.1	-
Diacetone alcohol	99	0.1	0.01	-	0.01 max.	25	mild	0.938 - 0.941	145 - 172	0.1	4,320	2.9	137	82	2.3	0.6	-
2,4-Pentanedione	99 min.	0.2	0.2	-	-	150	no odor requirement	0.972 - 0.975	-	-	-	-	-	-	-	-	-
4-Methoxy-4-methyl-2-pentanone	98.5	-	-	-	-	-	-	-	157 - 162	0.2	21,750	1.2	60	91	3.1	0.9	7.88
Cyclohexanone	99.8	0.05 max.	0.01 max. (as adipic acid)	0.07 max. as cyclohexanol	-	10	no odor requirement	0.946 - 0.949	1.0 max. including 155.5 ± 0.1	0.3	1,720	2.0	74	92	-	-	-
Isophorone	99.0 min.	0.01	0.10	-	-	100	mild	0.9210-0.9230	210 - 218	0.03	2,760	2.3	97	97	6.2	-	7.67
Acetophenone	97.0 min.	-	0.02 as benzoic acid	-	-	15	mild and aromatic	1.027 - 1.031	194 - 206	-	-	-	-	-	-	-	-

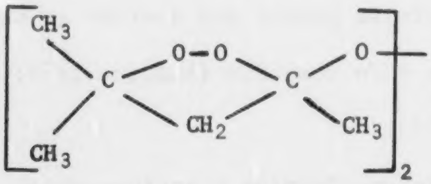
---

(a) The sample shall be completely miscible with the indicated volume of 60° API gasoline at 20°C (Union Carbide, 1968)
(b) At 25°, 0% relative humidity

Acidity ranges from a high of 0.02% by weight (as acetic acid) in 2,4-pentanedione to a low of 0.003% by weight found in methyl ethyl ketone. Another frequently occurring contaminant is water. Concentrations vary from a high of 0.3%, as in ethyl butyl ketone, to a low of 0.05% by weight in cyclohexanone. The alcohol concentration is as high as 4.0% by weight, which is found in trimethylnonanone. The presence of non-volatile substances and suspended matter is extremely low (i.e., between 0.001 - 0.005 g/100 mℓ (Union Carbide, 1968; Lurie, 1966).

In analysis of the impurities in a commercial grade (97.5 - 98%) of methyl ethyl ketone, fourteen individual oxygen containing impurities were found. The impurities included acetic acid, acetaldehyde, sec-butanol, and methyl vinyl ketone (Lebedeva et al., 1974).

The ketones are stable on standing with the exception of mesityl oxide. In prolonged contact with air, a peroxide forms. Since the peroxide is explosive, mesityl oxide is hazardous if distilled to dryness. Diisopropyl amine is sometimes added as a stabilizer (Lurie, 1966).



Peroxide of Mesityl Oxide

B. Chemistry

1. Reactions Involved in Use

a. Ketone Forming Reactions

The chemistry for commercially significant production of the selected ketones is summarized in Table 8. The production is further discussed in "Production Methods and Processes" (p. 56). MEK and the linear ketones are formed by the dehydrogenation of the corresponding alcohol over a solid catalyst, Reaction _2_; zinc oxide and thoria are commonly used dehydrogenation catalysts (Faith _et al._, 1965, Austin, 1974). MEK and cyclohexanone can be formed by the liquid phase oxidation of _n_-butane and cyclohexane, respectively, with oxidation catalysts such as cobalt or manganese salts, Reaction _1_ (Faith _et al._, 1965; Austin, 1974). Cyclohexanone and methylcyclohexanone are formed by hydrogenating phenol or methylphenol, Reaction _3_. Supported metals are the usual catalysts (Austin, 1974). The selected branched chain ketones are produced by ketone condensation and subsequent reactions outlined in Reaction _5_ (Oosterhof, 1967).

Oxidation of alkyl benzene yields a hydroperoxide which can subsequently be decomposed to phenol and ketone, Reaction _4_. While cumene hydroperoxide yields phenol and acetone as the major products, acetophenone is formed as a side reaction (Austin, 1974; Lederman and Poffenberger, 1968; Dorsky _et al._, 1963).

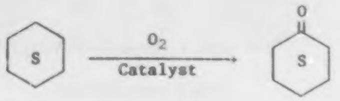
Ketone forming reactions which are not commercially important are tabulated in "Other Chemistry" (p. 38).

Table 8. Reactions for Selected Ketone Production
(From Austin, 1974; Faith et al., 1965; Lurie, 1966; Dorsky et al., 1963; Oosterhof, 1967)

1. **Aliphatic hydrocarbon oxidation:** methyl ethyl ketone (a) and cyclohexanone (b)

(a) $CH_3(CH_2)_2CH_3 \xrightarrow[\text{Catalyst}]{O_2} CH_3COCH_2CH_3$

(b)



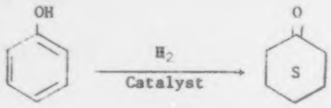
2. Alcohol dehydration or oxidation: methyl ethyl ketone and other linear ketones

(a) $RCH{=}CH_2 \xrightarrow[\text{Acid}]{H_2O} RCHOHCH_3$

(b) $RCHOHCH_3 \xrightarrow{\text{Catalyst}} RCOCH_3 + H_2$

(c) $RCHOHCH_3 \xrightarrow[\text{Catalyst}]{O_2} RCOCH_3 + H_2O$

3. Phenol hydrogenation



4. Alkyl aromatic hydrocarbon oxidation: acetone (major), acetophenone (minor)

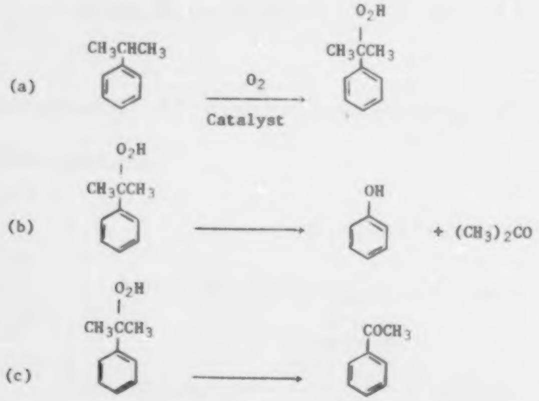
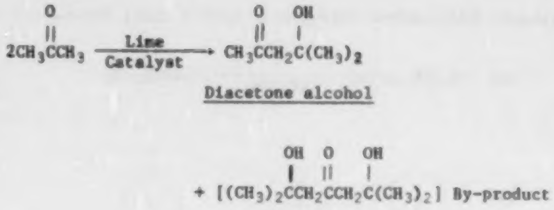


Table 8. (cont'd)

5. **Condensation products from acetone: methyl isobutyl ketone; diacetone alcohol; mesityl oxide: diisobutyl ketone; isophorone; trimethylnonanone; methyl isoamyl ketone.**

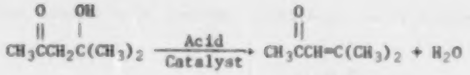


(a) $2CH_3\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[\text{Catalyst}]{\text{Lime}} CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{OH}{|}}{C}(CH_3)_2$

Diacetone alcohol

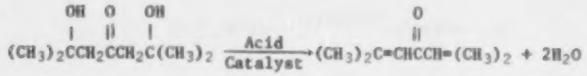
$+ [(CH_3)_2\overset{\overset{OH}{|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{OH}{|}}{C}(CH_3)_2]$ By-product

Triacetone alcohol



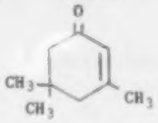
(b) $CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{OH}{|}}{C}(CH_3)_2 \xrightarrow[\text{Catalyst}]{\text{Acid}} CH_3\overset{\overset{O}{\|}}{C}CH{=}C(CH_3)_2 + H_2O$

Mesityl oxide

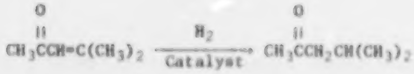


(c) $(CH_3)_2\overset{\overset{OH}{|}}{C}CH_2\overset{\overset{O}{\|}}{C}CH_2\overset{\overset{OH}{|}}{C}(CH_3)_2 \xrightarrow[\text{Catalyst}]{\text{Acid}} (CH_3)_2C{=}CH\overset{\overset{O}{\|}}{C}CH{=}(CH_3)_2 + 2H_2O$

Phorone

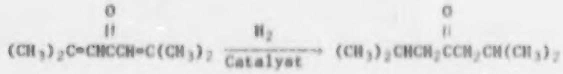


Isophorone



(d) $CH_3\overset{\overset{O}{\|}}{C}CH{=}C(CH_3)_2 \xrightarrow[\text{Catalyst}]{H_2} CH_3\overset{\overset{O}{\|}}{C}CH_2CH(CH_3)_2$

Methyl isobutyl ketone



(e) $(CH_3)_2C{=}CH\overset{\overset{O}{\|}}{C}CH{=}C(CH_3)_2 \xrightarrow[\text{Catalyst}]{H_2} (CH_3)_2CHCH_2\overset{\overset{O}{\|}}{C}CH_2CH(CH_3)_2$

Diisobutyl ketone

6. Benzophenone by the Friedel-Crafts reaction

(a) $2C_6H_6 + CCl_4 \xrightarrow[\text{AlC}_3]{} (C_6H_5)_2CCl_2 + 2HCl$
or other
Lewis acid

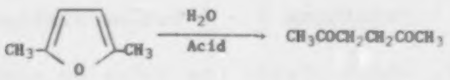
(b) $(C_6H_5)_2CCl_2 + H_2O \longrightarrow (C_6H_5)_2CO + 2HCl$

Table 8. (cont'd)

7. 2,4-Pentanedione by acylation of acetone

$$CH_3COCH_3 + (CH_3CO)_2O \xrightarrow[\text{or other Lewis acid}]{BF_3} CH_3COCH_2COCH_3 + CH_3CO_2H$$

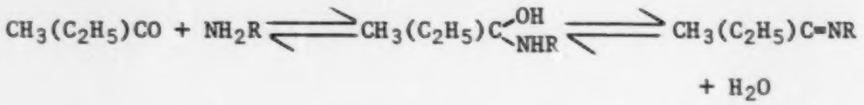
8. 2,5-Hexandione by 2,5-dimethylfuran hydrolysis


CH3
O
CH3
H2O
Acid
CH3COCH2CH2COCH3

b. Reactions of Ketones

Table 9 summarizes the important chemical reactions of ketones consumed as synthetic intermediates. A relatively small number of the possible reactions are commercially significant, since the major application (solvents) is dependent upon the physical properties of the materials. Other, less important chemistry is presented in Table 19 (p. 39).

Reactions 2 - 4 follow similar pathways. An intermediate amino alcohol forms, which yields the imine on dehydration. In the amine formation, reaction 4, the imine is reduced to the amine, and the entire sequence is carried out within a single reaction vessel. In the ε-caprolactam synthesis, the oxime formation and rearrangement must be carried out in separate reaction stages. This oxime reaction is commonly known as the "Beckman rearrangement" (Kralovec and Louderback, 1965).



$$\mathrm{CH_3(C_2H_5)CO + NH_2R \rightleftharpoons CH_3(C_2H_5)C}\begin{smallmatrix}\mathrm{OH}\\ \mathrm{NHR}\end{smallmatrix} \rightleftharpoons \mathrm{CH_3(C_2H_5)C{=}NR} \\ + \mathrm{H_2O}$$

Nitric acid oxidizes cyclohexanone to adipic acid. The oxidation sequence is carried out in a single stage reactor (Standish and Abramo, 1963). The sequence is thought to proceed via the intermediate nitrate, as follows (Cram and Hammond, 1964):

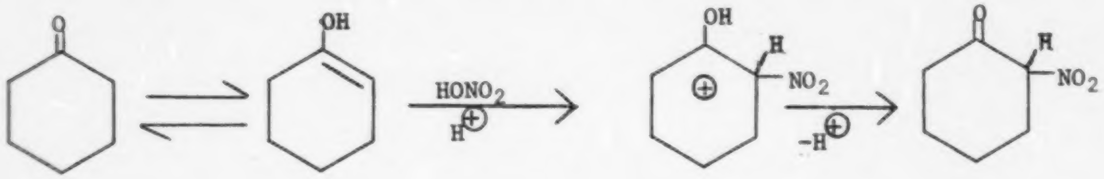
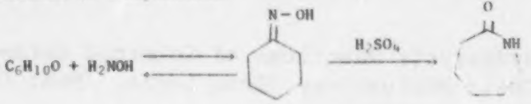


Table 9. Chemistry Important to Ketone Use (From Lurie, 1966; Standish and Abramo, 1963; Austin, 1974; Leston, 1971; Dorsky *et al*., 1963)

1. Cyclohexanone to adipic acid

$$C_6H_{10}O + HNO_3 \xrightarrow[\substack{100°C \\ 150\ psi}]{V_2O_5} HO_2C(CH_2)_4CO_2H$$

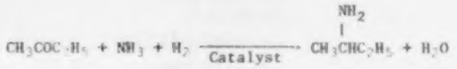
2. Cyclohexanone to ε-caprolactam


$C_6H_{10}O + H_2NOH$
N-OH
H_2SO_4
O
NH

3. Methyl ethyl ketoxime

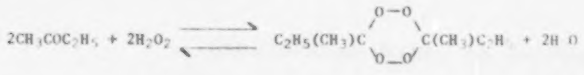
$$CH_3COC_2H_5 + H_2NOH \rightleftharpoons CH_3\overset{\overset{N-OH}{\|}}{C}C_2H_5 + H_2O$$

4. Amine formation (e.g. sec. - butylamine)

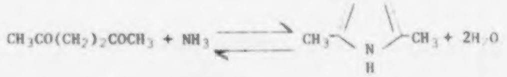


$$CH_3COC_2H_5 + NH_3 + H_2 \xrightarrow[Catalyst]{} CH_3\overset{\overset{NH_2}{|}}{C}HC_2H_5 + H_2O$$

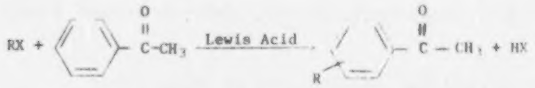
5. Methyl ethyl ketone peroxide


$2CH_3COC_2H_5 + 2H_2O_2$
$C_2H_5(CH_3)C$
O—O
O—O
$C(CH_3)C_2H_5$ + $2H_2O$

6. Reactions of diketones to cyclic derivatives

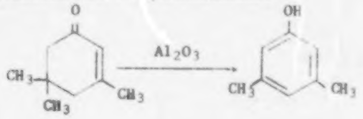

$CH_3CO(CH_2)_2COCH_3 + NH_3$
CH_3
N
H
CH_3 + $2H_2O$

7. Aromatic substitution


RX +
O
C-CH_3
Lewis Acid
O
C — CH_3 + HX
R

Where R = alkyl, acyl, etc.

8. Aromatization of cyclohexanones


O
CH_3
CH_3
CH_3
Al_2O_3
OH
CH_3
CH_3

2. Hydrolysis

Most of the selected ketones only participate in hydrolysis reactions at the carbonyl function. The hydration of the carbonyl, which is catalyzed both by acid and base, yields gem-diols. While gem-diols are not stable enough to be isolated, the related ethers (ketals and hemiketals) and other derivatives can be. Table 10 summarizes some of the hydrolysis reactions of the ketones and the related derivatives.

Table 10. Hydrolysis Reactions of Selected Ketones and Their Derivatives (From Lurie, 1966; Cram and Hammond, 1964)

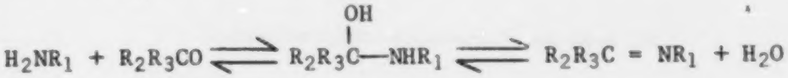
1) Addition of HX to the carbonyl

(a) $HX + R_1R_2CO \rightleftharpoons R_1R_2CX(OH)$

(b) $HX + R_1R_2CX(OH) \rightleftharpoons R_1R_2CX_2 + H_2O$

H-X	Product	
	From (a)	From (b)
H-OH	gemdiol	
H-CN	cyanohydrin	
H-NaSO$_3$	bisulfite	
H-OR(R=alkyl)	hemiketal	ketal
H-SR(R=alkyl)	hemithioketal	thioketal

2) Formation of imine derivatives

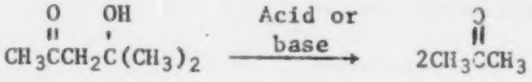


$$H_2NR_1 + R_2R_3CO \rightleftharpoons R_2R_3\overset{OH}{\overset{|}{C}}—NHR_1 \rightleftharpoons R_2R_3C = NR_1 + H_2O$$

For R_1 = H, alkyl, aryl, -OH, and -NHR$_4$, with R_4 = H, alkyl, aryl, -CONH$_2$

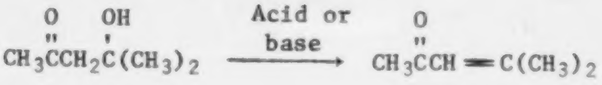
3) Reversible condensation vs. dehydration reactions of ketals

(a) Reversible condensation reaction



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{OH}{C}(CH_3)_2 \xrightarrow{\text{Acid or base}} 2CH_3\overset{\overset{O}{\|}}{C}CH_3$$

(b) Dehydration reaction



$$CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{OH}{C}(CH_3)_2 \xrightarrow{\text{Acid or base}} CH_3\overset{\overset{O}{\|}}{C}CH=C(CH_3)_2$$

The ketal forming reactions, which are used to manufacture some of the branched chain ketones, are reversible reactions (see Table 8). For example, under acidic or basic conditions, diacetone alcohol can react by competing pathways to yield the dehydration product (mesityl oxide) or the starting product (acetone). Product formation depends upon reaction conditions. Little information on kinetics is available in the literature (House, 1965).

3. Oxidation

Most of the selected ketones are stable to oxygen at ambient temperatures. This is in marked contrast to the related aldehydes which are slowly oxidized to carboxylic acids. A notable exception is mesityl oxide which forms an explosive peroxide (see p. 17).

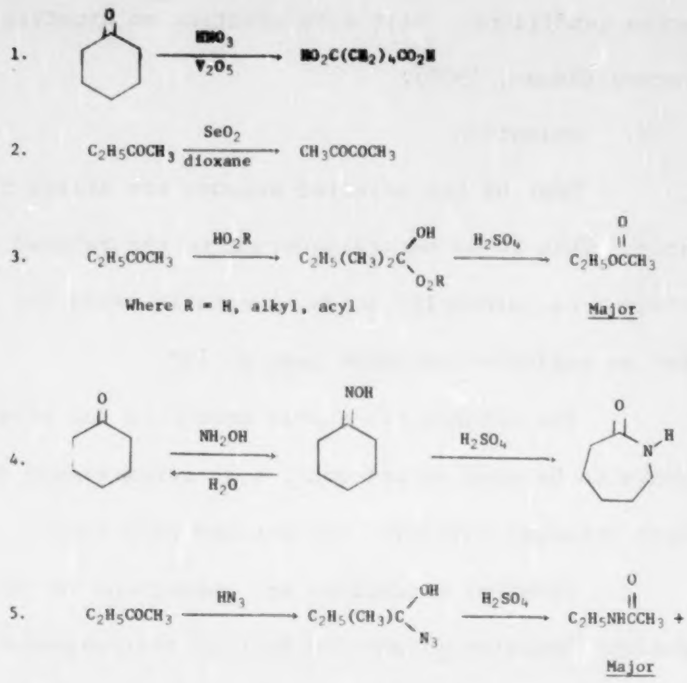
The ketones are stable enough in the presence of mild oxidizing agents to be used as solvents, e.g. permanganate oxidations (Lurie, 1966). With stronger oxidants, the ketones will react.

Chemical oxidations are summarized in Table 11. The nitric acid oxidation (Reaction 1) and the Beckman rearrangement (Reaction 4) are commercially important (see Table 9). Oxidants other than nitric acid, which are also capable of cleaving the cyclohexanone ring, include chromic acid and permanganate (Royals, 1961).

Aqueous halogenation proceeds to different products in acidic and basic solution and when unsymmetrical aliphatic ketones starting material are used. In acid solutions, the ketone yields a monohalo derivative at the more highly substituted α-carbon (Reaction 6a). In basic solution, the perhalo derivative is formed at the less substituted α-carbon (Reaction 6b).

Methyl ketones react *via* the haloform reaction (Reaction *6*c) to form haloform and a carboxylic acid. This reaction is a specific test for the methyl ketones. Because of the concern over chloroform in drinking water (Dowty *et al.*, 1975), this is a reaction of environmental concern.

Table 11. Chemical Oxidation of Selected Ketones
(Cram and Hammond, 1964)


1.
HNO3
V2O5
HO2C(CH2)4CO2H
2.
C2H5COCH3
SeO2
dioxane
CH3COCOCH3
3.
C2H5COCH3
HO2R
C2H5(CH3)2C(OH)O2R
H2SO4
C2H5OCCH3
Where R = H, alkyl, acyl
Major
4.
NH2OH
H2O
NOH
H2SO4
N
H
5.
C2H5COCH3
HN3
C2H5(CH3)C(OH)N3
H2SO4
C2H5NHCCH3 + N2
Major

6. Halogenation (R = alkyl groups)

(a) Acidic conditions

$$R_2CHCOCH_2R + X_2 \xrightarrow[H_2O]{} R_2CX\overset{O}{\overset{\|}{C}}CH_2R + HX$$

(b) Alkaline conditions

$$R_2CHCOCH_2R + 2X_2 \xrightarrow[H_2O]{} R_2CHCOCX_2R + 2HX$$

(c) Haloform reaction (alkaline conditions)

$$RCOCH_3 + 3X_2 \xrightarrow[H_2O]{} RCO_2H + CHX_3 + 3HX$$

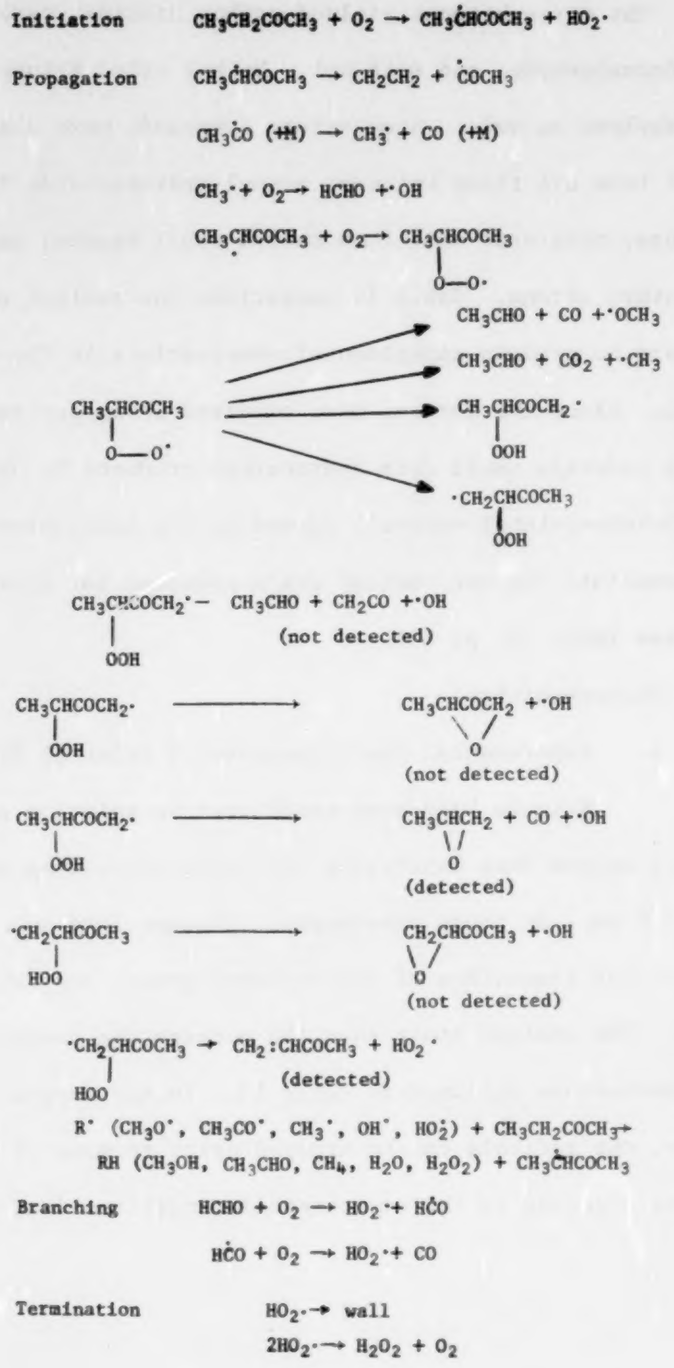
Barnard (1968) reported the products and reaction pathways for the oxidation of acetone, methyl ethyl ketone, and diethyl ketone in hot and cool flames. The three ketones yielded carbon dioxide, carbon monoxide, water, methane, formaldehyde, and methanol. Methyl ethyl ketone and diethyl ketone yielded ethylene as well. Some peroxy compounds were also produced: hydrogen peroxide from all three ketones; methyl hydroperoxide from acetone and methyl ethyl ketone; peracetic acid from methyl ethyl ketone; and ethyl hydroperoxide from diethyl ketone. Table 12 summarizes the radical chain sequence proposed by Barnard to explain experimental observations in the methyl ethyl ketone combustion. Since the ketones were oxidized in oxygen-poor atmospheres, some of the alkyl radicals could form hydrocarbon products by hydrogen transfer reactions. The 3-keto-2-butyl radicals formed in the initiation step are similar to the intermediate for the radical chain proposed for diethyl ketone photooxidation (see Table 15, p. 32).

4. Photochemistry

a. Experimental Photochemistry of Selected Ketones

Ketones have been photolyzed in solution and in the vapor phase, using oxygen-free conditions and light containing wavelengths from 253.7 to 313.0 nm. At these wavelengths, ketones form an excited singlet state from an $n \longrightarrow \pi^*$ transition of the carbonyl group (see Table 5, p. 12 and Figure 3, p. 11). The excited state then can undergo the possible energy transitions and fragmentations outlined in Table 13. In the oxygen rich conditions of the atmosphere, the radicals can be trapped prior to many of the transitions and fragmentations observed in the experimental conditions (see Table 15).

Table 12. Proposed Free Radical Chain Oxidation of Methyl Ethyl Ketone (Barnard, 1968)



Initiation $CH_3CH_2COCH_3 + O_2 \rightarrow CH_3\dot{C}HCOCH_3 + HO_2\cdot$

Propagation $CH_3\dot{C}HCOCH_3 \rightarrow CH_2CH_2 + \dot{C}OCH_3$

$CH_3\dot{C}O\ (+M) \rightarrow CH_3\cdot + CO\ (+M)$

$CH_3\cdot + O_2 \rightarrow HCHO + \cdot OH$

$CH_3\underset{\cdot}{C}HCOCH_3 + O_2 \rightarrow CH_3\underset{O-O\cdot}{\underset{|}{CH}}COCH_3$

$CH_3\underset{O-O\cdot}{\underset{|}{CH}}COCH_3 \rightarrow CH_3CHO + CO + \cdot OCH_3$

$\rightarrow CH_3CHO + CO_2 + \cdot CH_3$

$\rightarrow CH_3\underset{OOH}{\underset{|}{CH}}COCH_2\cdot$

$\rightarrow \cdot CH_2\underset{OOH}{\underset{|}{CH}}COCH_3$

$CH_3\underset{OOH}{\underset{|}{CH}}COCH_2\cdot - CH_3CHO + CH_2CO + \cdot OH$ (not detected)

$CH_3\underset{OOH}{\underset{|}{CH}}COCH_2\cdot \longrightarrow CH_3CHCOCH_2\ (\text{epoxide, }O) + \cdot OH$ (not detected)

$CH_3\underset{OOH}{\underset{|}{CH}}COCH_2\cdot \longrightarrow CH_3CHCH_2\ (\text{epoxide, }O) + CO + \cdot OH$ (detected)

$\cdot CH_2\underset{HOO}{\underset{|}{CH}}COCH_3 \longrightarrow CH_2CHCOCH_3\ (\text{epoxide, }O) + \cdot OH$ (not detected)

$\cdot CH_2\underset{HOO}{\underset{|}{CH}}COCH_3 \rightarrow CH_2{:}CHCOCH_3 + HO_2\cdot$ (detected)

$R\cdot\ (CH_3O\cdot, CH_3CO\cdot, CH_3\cdot, OH\cdot, HO_2\cdot) + CH_3CH_2COCH_3 \rightarrow RH\ (CH_3OH, CH_3CHO, CH_4, H_2O, H_2O_2) + CH_3\dot{C}HCOCH_3$

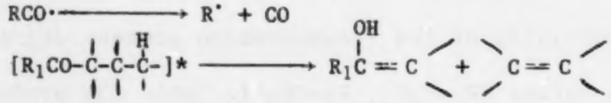
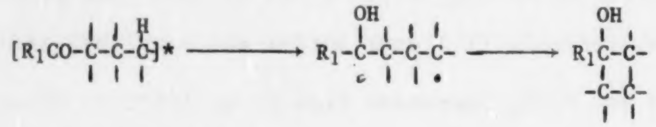
Branching $HCHO + O_2 \rightarrow HO_2\cdot + H\dot{C}O$

$H\dot{C}O + O_2 \rightarrow HO_2\cdot + CO$

Termination $HO_2\cdot \rightarrow \text{wall}$

$2HO_2\cdot \rightarrow H_2O_2 + O_2$

Table 13. Primary Photochemical Processes of Ketones (From Calvert and Pitts, 1966; Borrell and Bendlar, 1970; Pavlik et al, 1973; Lissi et al, 1974; Zahra and Noyes, 1965; Flood et al, 1974; Abuin et al, 1973.)

(a)	$R_1COR_2 + h\upsilon \longrightarrow {}^1[R_1COR_2]^*$	Singlet
(b)	${}^1[R_1COR_2]^* \longrightarrow {}^3[R_1COR_2]^*$	Triplet crossover
(c)	${}^1[R_1COR_2]^* \longrightarrow R_1COR_2 + h\upsilon$	Decay
(d)	${}^1[R_1COR_2]^* + M \longrightarrow R_1COR_2 + M$	Singlet quenching
(e)	${}^3[R_1COR_2]^* + M \longrightarrow R_1COR_2 + M$	Triplet quenching
(f1)	$[R_1COR_2]^* \longrightarrow R_1^{\cdot} + R_2CO^{\cdot}$	Norrish "Type I"
(f2)	$[R_1COR_2]^* \longrightarrow R_2^{\cdot} + R_1CO\cdot$	
(g)	$RCO\cdot \longrightarrow R^{\cdot} + CO$	
(h)	 $[R_1CO{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{H}{\underset{\mid}{C}}{-}]^* \longrightarrow R_1\overset{OH}{C}{=}C\!< \;+\; >\!C{=}C\!<$	Norrish "Type II"
(i)	 $[R_1CO{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{H}{\underset{\mid}{C}}]^* \longrightarrow R_1{-}\overset{OH}{\underset{\cdot}{C}}{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{\mid}{\underset{\mid}{C}}{-}\overset{\mid}{\underset{\cdot}{C}}{-} \longrightarrow \begin{array}{c} R_1\overset{OH}{C}{-}C{-} \\ \mid \quad \mid \\ {-}C{-}C{-} \end{array}$	
(j)	$[CH_3COCH(CH_3)_2]^* \longrightarrow CH_3CHO + C_3H_6$	Norrish "Type III"
(k)	$[CH_3COCH_3]^* \longrightarrow CH_3COCH_2^{\cdot} + H\cdot$	

The primary processes in fragmentation are fairly well defined. The Norrish "Type I" and "Type II" fragmentations (Table 13, Reactions f and h, respectively) are the major fragmentation processes in experimental photochemistry and are both thought to be important in atmospheric reactions. Either the singlet or triplet excited states can fragment by these two pathways (Dougherty, 1965; Wagner and Hammond, 1965). Other fragmentation possibilities exist (e.g., reactions j and k), but they are minor and will be negligible under atmospheric conditions (Zahra and Noyes, 1965; Calvert and Pitts, 1966).

Since the carbon-carbon bond cleavage in the Type I reaction of unsymmetrical ketones prefers formation of the more substituted alkyl radical, the preferred alkyl radical increases in the order methyl, primary, secondary, and tertiary. As the excited state energy is increased (irradiation at shorter wavelengths), the selectivity of the fragmentation process decreases. For example, methyl ethyl ketone (R_1=C_2H_5, R_2=CH_3 in Table 13) prefers to fragment to ethyl and acetyl radicals (f_1) over methyl and propionyl radicals (f_2). With irradiation at 313 nm, f_1/f_2 increases from 21 at 175°C to 40 at 100°C. At 100°C, selectivity changes with wavelength as follows: 40 at 313.0 nm, 5.5 at 265.4 nm and 2.4 at 253.7 (Calvert and Pitts, 1966). Since sunlight cuts off below 290 nm, a fairly high selectivity is expected in the atmospheric reactions.

Substrates can quench the ketone's triplet or singlet excited states (Table 13, reactions _d_ and _e_). The transferred energy can initiate fragmentation reactions in the receptor molecules. For example, the triplet states of benzophenone, acetophenone and aliphatic ketones can sensitize protein and DNA and initiate cleavage reactions (Rahn _et al._, 1974; Galardy _et al._, 1973). The end result for the excited ketone is its return to the ground state without any photochemical alterations occurring.

When simple ketones are irradiated in oxygen containing atmospheres, the free radicals produced by Norrish "Type I" reactions are rapidly trapped by the oxygen. The peroxy radicals which result then participate in a radical chain oxidation similar to that observed in slow combustion (Hoare and Whytock, 1967a, b; Kallend and Pitts, 1969). Kallend and Pitts' examination of diethyl ketone photooxidation has best elucidated the sequence of reactions. They examined the products from gas phase irradiation using 313.0 nm light, ketone pressure maintained at 20.0 mm, and an oxygen pressure ranging from 0 to more than 100 mm. The products and their quantum yields are recorded in Table 14. Even at low oxygen pressures, the photooxidation products did not contain any saturated hydrocarbons, as long as the gases were well mixed. This contrasts with the observation in slow combustion of diethyl ketone (Barnard, 1968). If the irradiated gases were poorly mixed, then saturated hydrocarbons were found. It is concluded that oxygen traps alkyl radicals before they can abstract any hydrogens. Kallend and Pitts (1969) have assigned the radical-chain sequence in Table 15 to the ketone photooxidation.

Table 14. Typical Relative Product Yields From Diethyl Ketone Photooxidation [a] (From Kallend and Pitts, 1969)

Product	Quantum yield (ϕ)
Acetaldehyde	3.4
Carbon dioxide	2.7
Ethanol	2.4
Carbon monoxide	1.1
Methanol	0.4 at high conversion
Ethylene	0.16
Water	0.15 product of thermal reaction
Ethylene oxide	0.01
Ethyl propionate	0.01
Ethyl vinyl ketone	0.01
Propionic acid	0.02
Perpropionic acid	0.1
Other acidic products	Traces at high conversion

---

[a] Photolysis of 20 mm of DEK + 1.0 mm of O_2 at 120° using 313.0 mm irradiation

Table 15. Free Radical Chain Mechanism Proposed for the Vapor Phase Photooxidation of Diethyl Ketone (at 313 nm) (From Kallend and Pitts, 1969)

Initiation

$$C_2H_5COC_2H_5 + h\nu \rightarrow C_2H_5CO\cdot + C_2H_5\cdot$$

Propagation and chain branching

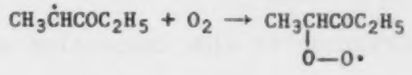
$$C_2H_5CO\cdot \longrightarrow C_2H_5\cdot + CO$$

$$C_2H_5\cdot + O_2 \rightarrow C_2H_5OO\cdot$$

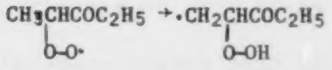
$$C_2H_5CO\cdot + O_2 \rightarrow C_2H_5O\cdot + CO_2$$

$$C_2H_5O\cdot + C_2H_5COC_2H_5 \rightarrow C_2H_5OH + CH_3\dot{C}HCOC_2H_5$$

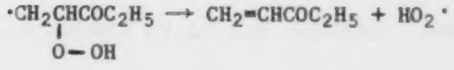
$$CH_3\dot{C}HCOC_2H_5 + O_2 \rightarrow CO_2 + CH_3CHO + C_2H_5\cdot$$



$$CH_3\dot{C}HCOC_2H_5 + O_2 \rightarrow CH_3\underset{\displaystyle O{-}O\cdot}{\underset{|}{C}}HCOC_2H_5$$



$$CH_3\underset{\displaystyle O{-}O\cdot}{\underset{|}{C}}HCOC_2H_5 \rightarrow \cdot CH_2\underset{\displaystyle O{-}OH}{\underset{|}{C}}HCOC_2H_5$$



$$\cdot CH_2\underset{\displaystyle O{-}OH}{\underset{|}{C}}HCOC_2H_5 \rightarrow CH_2{=}CHCOC_2H_5 + HO_2\cdot$$

$$2C_2H_5OO\cdot \rightarrow 2C_2H_5O\cdot + O_2$$

$$C_2H_5O\cdot + O_2 \rightarrow HO_2\cdot + CH_3CHO$$

Termination

$$HO_2\cdot + C_2H_5OO\cdot \rightarrow C_2H_5OOH + O_2$$

$$2C_2H_5O\cdot \rightarrow CH_3CHO + C_2H_5OH$$

b. Photochemical Smog Studies

The photochemical reactivity of hydrocarbons and other atmospheric, organic contaminants is measured and ranked using smog indicating parameters. Altshuller (1966) defines reactivity as "the tendency of an atmospheric system containing organic substances and nitrogen oxides to undergo, [under] the influence of U.V. radiation and appropriate meteorological conditions, a series of chemical reactions that result in the various manifestations associated with the photochemical type of air pollution."

The following parameters have been used to measure reactivity: rate of disappearance of the organic substrate of interest or of nitric oxide; production and maximum concentrations of oxidants (ozone and others), peroxyacylnitrates (PAN), formaldehyde, and other hydrocarbons; eye irritation; plant damage; and aerosol formation. According to Levy (1973), the most important parameters are oxidant formation and eye irritation.

The basic technique for reactivity measurement is to irradiate a mixture of the organic substrate of interest, nitric oxide and air in a smog chamber using a light source which simulates natural sunlight. Gross differences in measured values are often observed between laboratories. These result from differences in reactor design, reactor wall linings, light sources, and other causes (Jaffe and Smith, 1974; Bufalini et al., 1972; Altshuller and Bufalini, 1965, 1971). Table 16 compares some measurements taken at the Battelle-Columbus and Stanford Research Institute laboratories. The eight organic solvents examined include four ketones: methyl ethyl ketone (MEK), methyl isobutyl ketone (MIBK), cyclohexanone, and diacetone alcohol. A few sizable differences are observed.

Table 16. Comparison of Some Photochemical Smog Reactivity Parameters Measured at Different Laboratories [a] (From Levy, 1973)

	Oxidant-Maximum, ppm (Ranking Order)			Oxidant Dosage, ppm-min. (Ranking Order)		Eye-Irritation Response Time, sec. (Ranking Order)	
	BCL[b]	SRI[c]	SRI[d]	BCL[e]	SRI[f]	BCL[b]	SRI[c]
MIBK	0.45 (3)	0.13 (4)	0.34 (6)	267 (2)	36 (3)	213 (2)	162 (2)
MEK	0.28 (5)	0.13 (5)	0.35 (5)	232 (5)	21 (7,8,9)	295 (6)	201 (5)
Cyclohexanone	0.10 (6)	0.085(8)	0.31 (7)	262 (2)	21 (7,8,9)	309 (7,8)	193 (4)
Diacetone alcohol	0.60 (2)	0.24 (1)	0.40 (3,4)	193 (7)	62 (2)	214 (3)	188 (3)
Isopropyl alcohol	0.09 (7)	0.12 (6)	0.40 (3,4)	215 (6)	33 (5)	318 (9)	<240(7,8,9)
Isobutyl acetate	0.08 (8)	0.15 (3)	0.44 (2)	252 (4)	45 (4)	258 (5)	210 (6)
Diethyl Cellosolve	0.68 (1)	0.22 (2)	0.55 (1)	274 (1)	75 (1)	239 (4)	144 (1)
Toluene	0.44 (4)	0.08 (9)	- -	141 (9)	30 (6)	106 (1)	<240(7,8,9)
2-Nitropropane	0.07 (9)	0.10 (7)	- -	180 (8)	21 (7,8,9)	309 (7,8)	<240(7,8,9)
Air						280	<240

a. BCL = Battelle - Columbus Laboratory
   SRI = Stanford Research Institute
b. 4 ppm solvent/2 ppm NO.
c. 1 ppm solvent/0.1 ppm NO_x.
d. 8 or 4 ppm solvent/1 ppm NO_x, plus background mixture.
e. 4 ppm solvent/2 ppm NO, 6 hr dosage.
f. 1 ppm solvent/0.1 ppm NO_x, 7 hr dosage.

The results of a study on the reactivities of forty-five solvents, which was sponsored by the National Paint, Varnish, and Lacquer Association, are summarized in Table 17. The smog chamber measurements used mixtures of 4 ppm organic solvent and 2 ppm nitric oxide. Each of the solvents was rated from 1 to 3 for every measured parameter; Table 17 defines the rating system. With the exception of mesityl oxide (a branched chain olefin as well as a ketone), none of the ketones exceeded an average rating of 2.0. The ketones had low eye irritation and formaldehyde production ratings. While branched chain ketones were generally higher than straight chain ketones in oxidant production, they were similarly rated in NO_2 production. Four ketones (acetone, MEK, methyl isopropyl ketone, and cyclohexanone) had an average rating of 1.2 or less.

Smog production consists of a rather complex sequence of free-radical reactions, which involve inorganic and organic substrates. Several excellent reviews detail the proposed free-radical chain reactions and their contributions (Hecht et al., 1974; Altshuller and Bufalini, 1965, 1971). While there exists some experimental evidence on how the ketones participate in smog generation, much of the reasoning is based on ketone photolysis in oxygen-free atmospheres. While their relative contribution to overall smog generation has not been established, it is thought to be minor.

Ketones can participate in the photochemical smog cycle as free-radical chain initiators. Alkyl radicals, such as those generated in the Norrish "Type I" reaction of excited ketones, are known initiators (Haagen-Smit and Wayne, 1968; Laity, 1973). The photooxidation of acetone and 2-methyl-2-butene mixtures supports this supposition. The olefin disappears

Table 17. Summary of Photochemical Reactivity of Forty-Five Solvents [a] (Levy *et al.*, 1973)

Solvents	NO_2 t-Max	Oxidant Max	Eye Response	Formaldehyde	Averaged, Rating
Ketones					
Acetone	1	1	1	1	1
Cyclohexanone	1	1	1	1	1
Diacetone alcohol	2	3	1	1	1.7
Diisobutyl ketone	2	3	1	1	1.7
Di-*n*-propyl ketone	2	2	1	1	1.5
Isophorone	2	3	1	1	1.7
Mesityl oxide	3	3	2	2	2.5
Methyl *tert*-butyl ketone	3	3	1	1	2
Methyl isobutyl ketone	2	2	1	2	1.7
Methyl *n*-butyl ketone	2	2	1	1	1.5
Methyl ethyl ketone	2	1	1	1	1.2
Methyl *n*-propyl ketone	1	1	1	1	1.0
All other Solvents					
Benzene	1	1	1	1	1
trans-2-Butene	3	3	2	2	2.5
tert-Butylbenzene	2	1	1	1	1.2
Cumene	2	2	2	1	1.7
Cyclohexane	2	1	1	1	1.2
p-Cymene	3	2	1	1	1.7
Diethylamine	1	1	1	1	1
2-Ethoxyenthanol	2	3	1	1	1.7
Ethylbenzene	2	2	2	1	1.7
Ethylene	3	3	2	3	2.7
Isobutyl acetate	1	1	1	1	1
Isopropyl alcohol	1	1	1	1	1
Mesitylene	3	3	2	2	2.5
Methyl benzoate	1	1	1	1	1
N-Methyl pyrrolidone	2	3	1	1	1.7
α-Methylstyrene	3	3	3	3	3
Mineral spirits 7.5% ar.	2	2	1	1	1.5
14.6% ar.	2	2	1	1	1.5
15.0% ar.	2	2	1	1	1.5
16.0% ar.	2	2	1	1	1.5
19.8% ar.	2	3	1	1	1.7
53.1% ar.	3	3	2	1	2.2
2-Nitropropane	1	1	1	1	1
n-Octane	1	1	1	1	1
92% *n*-Octane/8% *m*-Xylene	2	2	1	1	1.5
80% *n*-Octane/20% *m*-Xylene	2	3	1	1	1.7
50% *n*-Octane/50% *m*-Xylene	3	3	2	1	2.2
Phenyl acetate	1	1	1	1	1
Styrene	2	2	3	2	2.2
Tetrahydrofuran	2	3	2	1	2
Toluene	2	2	2	1	1.7
Triethylamine	1	1	1	1	1
m-Xylene	3	2	2	1	2

[a]Reactivity Category	NO_2 t-Max, min	Oxidant Max, ppm	E.I. sec[a]	Formaldehyde, ppm
3 High reactivity	0-100	0.57-0.85	0-60	1.0-1.6
2 intermediate reactivity	101-200	0.29-0.56	61-160	0.5-1.0
1 low reactivity	201-360	0-0.28	161-360	0-0.5

[a] Eye response.

more rapidly from the ketone-olefin mixture (Altshuller and Bufalini, 1971). Results are summarized in Table 18.

Table 18. Photooxidation of Acetone (A) and 2-Methyl-2-butene (MB) in Air Mixtures by Sunlight Fluorescent Lamps (From Altshuller and Bufalini, 1971)

Initial Concentrations in ppm		Amount Reacted During Irradiation Percent at given times (minutes)						Products at 180 min. in ppm	
Acetone	2-Methyl-2-butene	60		120		180		Formaldehyde	Total Oxidant
		A	MB	A	MB	A	MB		
10	0	12.4		23.3		31.9		2.88	0.352
5	10	10.2	2.3	22.4	7.0	34.7	11.3	0.93	0.29
10	10	11.4	4.5	23.8	8.6	32.4	15.8	1.8	0.49
20	10	12.2	7.8	23.6	17.6	33.5	28.7	3.84	0.84

The acyl radicals produced in the Norrish "Type I" fragmentation can react with oxygen and nitrogen dioxide to yield peroxyacyl nitrates. Evidence supporting this scheme has been published by Laity *et al*. (1973). The irradiation of diethyl ketone and of *t*-butyl ethyl ketone in smog chambers yielded high concentrations (18 and 27 ppb, respectively) of peroxypropionyl nitrate and 36 and 23 ppb, respectively, of peroxyacetyl nitrate. The data suggest the following reaction scheme:

$$[C_2H_5COR]^* \longrightarrow C_2H_5CO\cdot + R\cdot$$

where R = C_2H_5 or *t*-C_4H_9

$$C_2H_5CO\cdot + O_2 \longrightarrow C_2H_5COO_2\cdot$$

$$C_2H_5COO_2\cdot + NO_2 \longrightarrow C_2H_5COO_2NO_2$$

Laity *et al*. (1973) have suggested that olefins produced by the Norrish "Type II" reaction would also participate in the conversion of NO to NO_2 and in the build-up of ozone and aldehyde. In support of their suggestion, they cite the slower reaction of cyclohexanone in smog chambers than other ketones with α-hydrogens. Cyclohexanone does not fragment by a "Type II" reaction because of its stereochemistry.

The abstraction of ketonic α-hydrogen atoms, such as observed in the free-radical oxidations (see Tables 12 and 14), can also be important in smog generation. When MIBK is irradiated in air without nitrogen oxides, ketone disappearance is less rapid and acetone production is low (Laity et al., 1973). This is excellent evidence that products formed through the inorganic reaction cycle are important to the ketone degradation. Since ozone and peroxide react relatively slowly with ketones, radical reactions in which the inorganic radicals are the hydrogen abstractors are suggested.

5. Other Chemistry

Although ketone chemistry includes a wide number of reactions, few of them are important either to their consumption or their environmental degradation. Table 19 lists many of the possible reactions.

Table 19. Miscellaneous Ketone Chemistry (From Lurie, 1966; Cram and Hammond, 1964; Roberts and Caserio, 1965; Royals, 1961; House, 1965)

Ketone forming reactions

1. From acyl derivatives

   (a) From acyl derivatives

$$RCOX + CH_2{=}CHR \xrightarrow[\text{or other Lewis acid}]{AlCl_3} RCOCH{=}CHR + HX$$

   (b) Grignard reactions

$$R_1COX + R_2MgX \xrightarrow[\text{Ether}]{} R_1COR_2 + MgX_2$$

   (c) Carboxylic acid condensation

$$R_1CO_2H + R_2CO_2H \xrightarrow[\text{catalyst}]{\text{metal}} R_1COR_2 + R_1COR_1 + R_2COR_2$$

2. Acetylene hydration

$$\text{(a)}\quad HC{\equiv}CH + NaNH_2 \xrightarrow{\text{Liq. } NH_3} HC{\equiv}C^{-}Na^{+} + NH_3$$

$$\text{(b)}\quad HC{\equiv}CNa + RX \longrightarrow HC{\equiv}CR + NaX$$

$$\text{(c)}\quad HC{\equiv}CR + H_2O \xrightarrow[\substack{H_2SO_4 \\ HgSO_4}]{} CH_3COR$$

3. Olefin ozonation

$$R_1R_2C{=}CR_3R_4 \xrightarrow[H_2O]{O_3} R_1R_2CO + R_2R_4CO$$

Ketone reactions

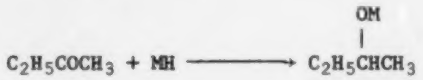
4. Catalytic hydrogenation over supported metals (such as Raney nickel)

$$C_2H_5COCH_3 + H_2 \xrightarrow{\text{Catalyst}} C_2H_5\overset{\overset{OH}{|}}{C}HCH_3$$

Table 19. (cont'd)

5. **Hydride transfer**

   (a) **From metal hydrides (such as $LiAlH_4$ and $NaBH_4$)**

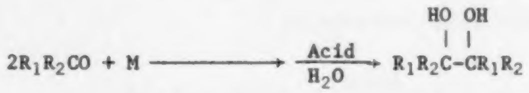


$$C_2H_5COCH_3 + MH \longrightarrow C_2H_5\overset{\displaystyle OM}{\overset{|}{C}}HCH_3$$

   (b) From aluminum isopropoxide (Meerwein, Ponndorf, Verley Reaction)

$$3C_2H_5COCH_3 + Al[OCH(CH_3)_2]_3 \longrightarrow [C_2H_5(CH_3)CHO]_3Al + (CH_3)_2CO$$

6. Reductive dimerization (M = sodium, potassium, magnesium)



$$2R_1R_2CO + M \longrightarrow \xrightarrow[H_2O]{Acid} R_1R_2\overset{\displaystyle HO}{\overset{|}{C}}-\overset{\displaystyle OH}{\overset{|}{C}}R_1R_2$$

7. Reduction to saturated carbon (Wolf-Kishner Reaction)

$$R_1R_2C{=}O + H_2NNH_2 \rightleftharpoons R_1R_2C{=}NNH_2 + H_2O$$

$$R_1R_2C{=}NNH_2 \xrightarrow[H_2O]{Base} R_1R_2CH_2$$

8. Halogenation

   (a) $R_1R_2CO + PCl_5 \longrightarrow R_1R_2CCl_2$

   (b) $R_1R_2CO + SF_4 \longrightarrow R_1R_2CF_2$

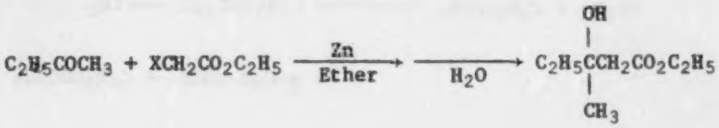
9. Condensation reactions

   (a) Claisen condensation

$$CH_3CH_2COCH_3 + C_2H_5CO_2C_2H_5 \xrightarrow{Base} \underset{\underline{Major}}{C_2H_5COCH_2COC_2H_5} + \underset{\underline{\mathbf{Minor}}}{CH_3COCH(CH_3)COC_2H_5}$$

Table 19. (cont'd)

(b) **Reformatsky Reaction (X = halogen)**



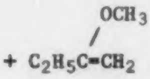
$$C_2H_5COCH_3 + XCH_2CO_2C_2H_5 \xrightarrow[\text{Ether}]{\text{Zn}} \xrightarrow[H_2O]{} C_2H_5\underset{\underset{CH_3}{|}}{\overset{\overset{OH}{|}}{C}}CH_2CO_2C_2H_5$$

(c) **With alkyl halides (carbonyl oxygen vs. α - carbon reactivity)**

$$C_2H_5COCH_3 \underset{H^+\ \text{Base}}{\overset{\text{Base}}{\rightleftarrows}} C_2H_5COCH_2^{\ominus}$$

$$C_2H_5COCH_2^{\ominus} + CH_3X \longrightarrow C_2H_5COCH_2CH_3$$

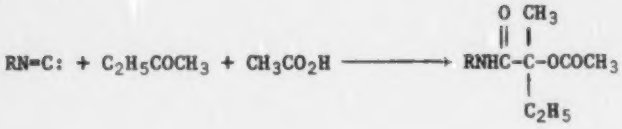
Major



$$+ \ C_2H_5\overset{OCH_3}{\overset{/}{C}}{=}CH_2$$

Minor

10. **With isocyanides**



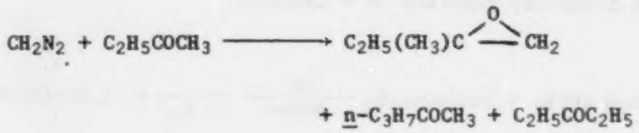
$$RN{=}C: + C_2H_5COCH_3 + CH_3CO_2H \longrightarrow RNH\overset{\overset{O}{\|}}{C}-\underset{\underset{C_2H_5}{|}}{\overset{\overset{CH_3}{|}}{C}}-OCOCH_3$$

11. **With alkidene phosphorines**

$$R_3PCH_2 + C_2H_5COCH_3 \longrightarrow C_2H_5\overset{\overset{CH_3}{|}}{C}{=}CH_2 + R_3PO$$

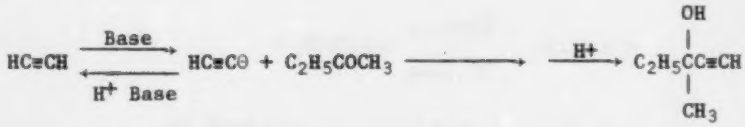
Table 19. (cont'd)

12. With diazomethane



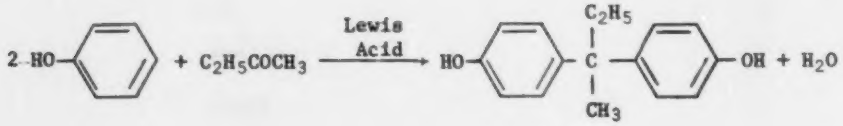
$$CH_2N_2 + C_2H_5COCH_3 \longrightarrow C_2H_5(CH_3)C\overset{O}{\frown}CH_2 + \underline{n}\text{-}C_3H_7COCH_3 + C_2H_5COC_2H_5$$

13. With acetylene



$$HC{\equiv}CH \underset{H^+\ \text{Base}}{\overset{\text{Base}}{\rightleftharpoons}} HC{\equiv}C^\ominus + C_2H_5COCH_3 \longrightarrow \xrightarrow{H^+} C_2H_5\overset{OH}{\underset{CH_3}{C}}C{\equiv}CH$$

14. With aromatics



2 HO
+ $C_2H_5COCH_3$
Lewis Acid
HO
C_2H_5
C
CH_3
OH + H_2O

II. Environmental Exposure Factors

A. Production Consumption

1. Quantity Produced

Of the selected ketones, quantitative data on production, sales, imports and exports are available for only seven: MEK; MIBK; diacetone alcohol; cyclohexanone; acetophenone; benzophenone; and acetone. Although acetone is not being considered in this study, its production data are of interest since it is a precursor of several other ketones including MIBK, diacetone alcohol, mesityl oxide and isophorone.

Table 20 reports production and sales figures for the seven ketones listed above; Table 21 summarizes their import and export data. The quantities in Table 20 refer only to U.S. production and sales. Net import and export of MEK and MIBK have a negligible effect on the market availability (USTC, 1971). Import and export of cyclohexanone, acetophenone and benzophenone were generally negligible (USITC, Annual b). A majority of the cyclohexanone is produced for captive consumption (SRI, 1973, 1974, 1975).

In 1968, seven ketones accounted for approximately 98% of the aliphatic ketones produced (excluding acetone and cyclohexanone). The seven were rated by the U.S. International Trade Commission (formerly U.S. Tariff Commission) in the following order of decreasing production: MEK; MIBK; diacetone alcohol; mesityl oxide; diisobutyl ketone; isophorone; and methyl isoamyl ketone (USTC, 1971). The USTC (1971) accounted for the remaining 2% primarily as ethyl amyl ketone; trimethylnonanone; 2,4-pentanedione (acetylacetone); and 2,5-hexanedione (acetonylacetone). Smaller amounts of methyl amyl ketone and diethyl ketone were also reported.

Table 20. U.S. Production and Sales of Selected Ketones (a)
(From USITC, Annual a)

	Acetone		Methyl ethyl ketone		Methyl isobutyl ketone		Diacetone Alcohol		Cyclohexanone		Acetophenone		Benzophenone	
Year	Production	Sales	Production	Sales	Production	Sales	Production	Sales	Production	Sales	Production	Sales	Production	Sales
1964	1,054,756	672,093	288,934	267,417	158,607	134,822	---	---	293,955	11,082	---	---	---	---
1965	1,124,097	741,665	317,500	301,161	168,864	151,027	---	28,004	321,651	12,269	---	---	179	122
1966	1,330,178	841,222	399,077	351,783	198,387	167,977	---	30,818	314,424	---	965	714	182	124
1967	1,283,978	827,739	400,424	381,782	199,274	155,294	---	31,643	429,457	17,422	1,773	1,191	261	132
1968	1,360,603	1,014,637	451,224	437,842	182,090	166,852	87,166	31,767	481,892	20,369	1,742	659	245	217
1969	1,518,380	1,078,472	484,372	423,708	200,511	164,986	77,511	33,863	704,215	58,874	---	1,174	191	129
1970	1,615,248	1,123,551	480,228	427,218	196,043	166,948	---	37,493	714,470	33,777	814	---	357	126
1971	1,538,322	1,098,983	483,790	471,760	191,813	157,341	---	37,678	756,472	46,494	---	---	407	159
1972	1,818,373	1,495,112	509,025	470,010	208,263	177,013	---	46,482	783,440	56,960	---	1,679	449	300
1973	1,989,469	1,547,689	540,709	520,126	154,751	168,909	---	50,994	638,156	45,937	2,246	1,752	741	426

(a) In thousands of pounds.

Table 21. U.S. Import and Export of Selected Ketones [(a)]
(From SRI, 1972a; USTC, 1971; USITC, Annual b)

Year	Acetone		Methyl ethyl ketone		"Other Ketones"		Cyclohexanone		Acetophenone	
	Export	Import	Export	Import	Export	Import	Export	Import	Export	Import
1964	44,082	8,463	---	---	---	---	---	---	---	---
1965	13,007	28,645	29,128	8,727	---	5,637	---	---	---	---
1966	8,671	57,680	32,717	12,556	---	6,420	---	---	---	---
1967	23,166	63,124	47,246	8,837	---	15,097	---	810	---	---
1968	21,633	71,225	33,175	18,296	---	15,501	---	---	---	---
1969	17,064	86,396	29,824	29,662	---	17,697	---	---	---	---
1970	---	---	22,100	33,000	---	---	---	---	---	---
1971	---	---	26,000	29,300	---	---	---	---	---	22
1972	---	---	---	---	---	---	---	---	---	---
1973	---	---	---	---	---	---	---	1,157	---	---

(a) In thousands of pounds.

Although production figures are not available for ketones other than those listed in Table 20, the 1973 production of three ketones (diacetone alcohol; isophorone; and mesityl oxide) can be estimated from acetone consumption data (see Table 22). Blackford (1975) estimated that each pound of MIBK produced required 1.25 pounds of acetone; this corresponds to a yield of slightly above 90%. The production of the other three ketones was calculated with the 90% yield estimate. The estimated diacetone alcohol production (43 million pounds) is about 20% lower than the reported sales (51 million pounds), and the MIBK estimation of 210 million pounds is 55 million pounds higher than the USITC figures (Table 20). While the values for isophorone and mesityl oxide might be poor estimates, they do place a perspective on their commercial importance.

Table 22. Estimated Production of Four Ketones Derived From Acetone in 1973 (From Blackford, 1975)

	In Millions of Pounds	
Ketone	Acetone Consumed for Production	Estimated Ketone Production[a]
Methyl isobutyl ketone	263	210
Diacetone alcohol	48	43
Isophorone	35	28
Mesityl oxide	27	22

(a) Approximately 90% yield from acetone is assumed.

2. Producers, Major Distributors, Importers, Sources of Imports and Production Sites

The producers and production site locations for the selected ketones are listed in Table 23. The distribution of plant locations is illustrated in Figure 6. Table 24 summarizes major producers of these ketones for the years 1965 to 1973.

Table 23 also lists plant capacities for three ketones: MEK; MIBK; and cyclohexanone. The capacities are quite flexible. Two plants, which manufacture MEK by butane oxidation (Celanese Corp. and Union Carbide Corp.), can adjust process conditions in order to produce MEK or acetic acid. Two other plants (Shell Chemical Co. and Enjay Chemical Co.) can produce either acetone or MEK (Stanford Research Institute (SRI), 1972a). The MIBK facilities can be adjusted to produce the related acetone derivative, methyl isoamyl ketone (Oosterhof, 1967). The data on cyclohexanone in Table 23 do not include a plant (Monsanto Company at Luling, La.) having a 25 million pound capacity for cyclohexanol (captive and merchant; synthesis via phenol reduction)(SRI, 1974). This plant could be used for production of cyclohexanone.

Construction of additional plant facilities for MEK will increase its capacity by 320 million pounds in 1977. Shell Chemical Co. anticipates the completion of a 230 million pound plant in Norco, La., by late 1977 (Chemical Marketing Reporter (CMR), 1975c). Exxon Chemical Co. will expand production at its Linden, N.J., plant from 210 to 300 million pounds; a major part of this expansion is expected on stream early in 1977 (Anon., 1975a). Universal Oil Products has also reported increasing capacity for benzophenone at its East Rutherford, N.J., plant (CMR, 1975d).

Table 23. Major Producers, Production Sites, and Annual Production Capacities of the Selected Ketones (From SRI, 1974, 1975)

Ketone	Producer	Plant Site	Capacity in millions of pounds 1974	1975	Process
Diethyl ketone	Aceto Chemical Co., Inc. Roehr Chemical Co., Inc. (subsidiary)	Long Island City, NY			
	Hexagon Laboratories, Inc.	Bronx, NY			
	Union Carbide Corp.	Institute and So. Charleston, WV			
	E.I. Dupont deNemours & Co.	Deepwater, NJ and Bronx, NY			
Di-n-propyl ketone	Aceto Chemical Co., Inc. Roehr Chemical Co., Inc. (subsidiary)	Long Island City, NY			
Diisobutyl ketone	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV			
Methyl ethyl ketone	Atlantic Richfield Co. ARCO Chemical Co., Div.	Channelview, TX	50	64	Dehydrogenation of sec-butyl alcohol
	Celanese Corp. Celanese Chem. Co., Div.	Pampa, TX	115	115	
	Dart Industries Aztec Chems.	Elyria, OH	---	n.a.	Butane oxidation
	Dixie Chemical Co.	Bayport, TX	n.a.	3	Butadiene by-product
	Eastman Kodak Co.	Kingsport, TN	n.a.	n.a.	
	Exxon Corporation Exxon Chem. Co., Div.	Bayway, NJ	210	200	
	Shell Chemical Co.	Deer Park, TX	100	100	Dehydrogenation of sec-butyl alcohol
		Martinez, CA	---	n.a.	
		Norco, LA	50	50	Dehydrogenation of sec-butyl alcohol
	Union Carbide Corp.	Brownsville, TX	75	60	Butane oxidation
		Total	600	592	
Methyl n-propyl ketone	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV			
Methyl n-butyl ketone	Eastman Kodak Co. Eastman Chemical Products, Inc.	Kingsport, TN			
Methyl isobutyl ketone	Eastman Kodak Co. Eastman Chemical Products, Inc.	Kingsport, TN	30 (25)^c	30	
	Exxon Corporation Exxon Chemical Co., Div.	Bayway, NJ	35 (40)^c	40	
	Shell Chemical Co. Industrial Chemical Div.	Deer Park, TX	80 (80)^c	80	
		Dominguez, CA	35 (16)^c	35	
	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV	60 (85)^c	65	
		Total	240 (246)^c	250	
Methyl n-amyl ketone	Eastman Kodak Co. Eastman Chemical Products, Inc.	Kingsport, TN			
	Lachat Chemical, Inc.	Chicago Heights, IL			
	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV			
Methyl n-hexyl ketone	Union Camp Corp. Harchem Div.	Dover, OH			
Ethyl n-butyl ketone	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV			
Mesityl oxide	Shell Chemical Co. Industrial Chem. Div	Deer Park, TX Dominguez, CA			
	Union Carbide Corp. Chemical & Plastics Div.	Institute and So. Charleston, WV			
Diacetone alcohol	Shell Chemical Co. Industrial Chem. Div.	Deer Park, TX Dominguez, CA			
	Union Carbide Corp.	Institute and So. Charleston, WV			
	Celanese Corp.	Pampa, TX			

Table 23. (cont'd)

Ketone	Producer	Plant Site	Capacity in millions of Pounds 1974	 1975	Process
4-Methoxy-4-methyl-2-pentanone	Shell Chemical Co. Base Chemicals	Martinez, CA			
3-Methylcyclohexanone	Frank Enterprises	Columbus, OH			
Cyclohexanone	Allied Chemical Corp. Plastic Div.	Hopewell, VA[d]	346	346	Phenol reduction
	Celanese Corp. Celanese Chem. Co. Div.	Bay City TX[e]	100	100	Cyclohexane oxidation
	Dow Badische Co.	Freeport, TX[e]	250	250	Cyclohexane oxidation
	El Paso Natural Gas Co. El Paso Products Co.	Odessa, TX[e]	64	64	Cyclohexane oxidation
	Monsanto Co. Monsanto Textiles Co.	Pensacola, FL[e]	500	500	Cyclohexane oxidation
	Nipro, Inc.	Augusta, GA[d]	150	150	Cyclohexane oxidation
	Rohm & Haas Co. Rohm & Haas Kentucky, Inc.	Louisville, KY[e]	40	40	Cyclohexane oxidation
	Union Carbide Corporation Chemical & Plastics Div.	Taft, LA[e]	70	70	Cyclohexane oxidation
		Total	1545	1545	
Isophorone	Union Carbide Corporation Chemical & Plastics Div.	Institute and So. Charleston, WV			
Methyl isoamyl ketone	Eastman Kodak Co. Eastman Chemical Products, Inc.	Kingsport, TN			
	Union Carbide Corp. Chemicals & Plastics Div.	Institute and So. Charleston, WV			
Ethyl amyl ketone	Givaudan Corp.	Clifton, NJ			
	Shell Chemical Co. Industrial Chem. Div.	Martinez, CA			
2,4-Pentanedione (Acetylacetone)	Mackenzie Chem. Works, Inc.	Central Islip, NY			
	Union Carbide Corp. Chemicals & Plastics Div.	Institute and So. Charleston, WV			
Trimethylnonanone (Isobutyl heptyl ketone)	Union Carbide Corp. Chemicals & Plastics Div.	Institute and So. Charleston, WV			
Acetophenone	Clark Oil & Refining Co. Clark Chemical Corp.	Blue Island, IL			
	Givaudan Corp. Chemical Div.	Clifton, NJ			
	Union Carbide Corp. Chemical & Plastics Div.	Bound Brook, NJ			
	Allied Chemical Corp.[f] Plastics Div.	Frankford, PA			
	Skelly Oil Co.	El Dorado, KS			
	Universal Oil Products Co.[f] Chemical & Plastics Group Chemical Div.	East Rutherford, NJ			
Benzophenone	Aceto Chemical Co., Inc.	Carlstadt, NJ			
	GAF Corp., Chemical Div.	Linden, NJ			
	Givaudan Corp.	Clifton, NJ			
	Norda Inc.	Boonton, NJ			
	Orbis Products	Newark, NJ			
	Parke, Davis & Co.	Detroit, MI			
	Universal Oil Products Co. Chemical Div	E. Rutherford, NJ			
	Neville-Synthese Organics, Inc.	Neville Island, PA			

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a. Exxon Chemical Company plans to expand capacity to 300 million pounds per year. Expected completion date in early 1977. (Anon., 1975)

b. Shell Chemical Company is reportedly constructing a 230 million pound plant in Norco, LA to be completed in late 1977. (Chemical Marketing Reporter, 1975c)

c. Chemical Marketing Reporter, 1975a

d. Captive and merchant

e. Captive

f. Technical grade

Table 24. Major Producers of Selected Ketones (1965 to 1973)

Year and Reference	Diethyl ketone				Di-n-propyl ketone	Diisopropyl ketone	Diisobutyl ketone		Methyl ethyl ketone								
	Aceto Chemical Co., Inc.	E.I. Dupont Co.	Hexagon Laboratories	Union Carbide Corp.	Aceto Chemical Co., Inc.	Eastman Kodak Co.	Eastman Kodak Co.	Union Carbide Corp.	ARCO Chemical Co. (a)	Sinclair Petrochemicals (a)	Celanese Corp.	Dart Industries	Dixie Chemicals	Eastman Kodak Co.	Exxon Corp.	Shell Chemical Co.	Union Carbide Corp.
S.R.I., 1975	X	X	X	X	X			X	X		X	X	X	X	X	X	X
S.R.I., 1974	X		X	X	X			X	X		X		X	X	X	X	X
U.S.I.T.C. Annual a																	
1973	X		X			X		X	X		X		X		X	X	X
1972	X		X			X		X	X		X		X		X	X	X
1971	X		X			X	X	X	X		X		X	X	X	X	X
1970							X	X	X		X		X	X	X	X	X
1969			X				X	X	X		X		X	X	X	X	X
1968			X				X	X		X	X		X		X	X	X
1967		X					X	X		X	X		X		X	X	X
1966			X				X	X		X	X		X		X	X	X
1965			X				X	X		X	X		X		X	X	X

X ˉ Listed in the reference.

(a) Merged

Table 24. (cont'd)

Year and Reference	Methyl n-propyl ketone	Methyl n-butyl ketone	Methyl isobutyl ketone					Methyl n-amyl ketone			Methyl isoamyl ketone		Methyl n-hexyl ketone		Trimethyl-nonanone	Ethyl n-butyl ketone
	Union Carbide Corp.	Eastman Kodak Co.	Celanese Corp.	Eastman Kodak Co.	Exxon Corp.	Shell Chemical Co.	Union Carbide Corp.	Eastman Kodak Co.	Lachat Chemical, Inc.	Union Carbide Corp.	Eastman Kodak Co.	Union Carbide Corp.	Union Camp Corp.	Universal Oil Products	Union Carbide Corp.	Union Carbide Corp.
S.R.I., 1975	X	X		X	X	X	X	X		X	X	X	X		X	X
S.R.I., 1974	X	X		X	X	X	X		X	X	X	X	X		X	X
U.S.I.T.C. Annual a																
1973	X		X	X	X	X	X			X	X				X	X
1972	X			X	X	X	X			X	X	X			X	X
1971	X			X	X	X	X			X	X	X			X	X
1970	X			X	X	X	X		X	X	X	X			X	X
1969				X	X	X	X			X	X	X			X	
1968				X	X	X	X			X	X	X			X	
1967				X	X	X	X			X	X	X			X	
1966	X			X	X	X	X			X	X	X		X	X	
1965	X			X	X	X	X			X	X	X			X	

Table 24. (cont'd)

Year and Reference	Ethyl n-amyl ketone			Mesityl oxide		Diacetone alcohol			4-Methoxy-4-methyl-2-pentanone	2,4-Pentanedione (acetylacetone)		2,5-Hexanedione (acetonylacetone)			
	Givaudan Corp.	Shell Chemical Co.	Union Oil Products	Shell Chemical Co.	Union Carbide Corp.	Celanese Corp.	Shell Chemical Co.	Union Carbide Corp.	Shell Chemical Co.	McKenzie Chemical Works, Inc.	Union Carbide Corp.	Aceto Chemical Co., Inc. (b)	Arsynco, Inc. (b)	Pike Chemicals Inc.	Union Carbide
S.R.I., 1975	X	X		X	X	X	X	X	X	X	X				
S.R.I., 1974	X	X		X	X	X	X	X	X	X	X				
U.S.I.T.C. Annual a															
1973		X		X	X	X	X	X	X		X		X		X
1972		X		X	X	X	X	X	X		X		X		
1971		X		X	X	X	X	X	X		X			X	X
1970				X	X	X	X	X	X		X			X	X
1969				X	X	X	X	X	X		X	X		X	X
1968				X	X	X	X	X	X		X	X		X	X
1967			X	X	X	X	X	X	X		X	X		X	X
1966				X	X	X	X	X	X		X			X	
1965				X		X	X	X	X		X	X		X	

(b) Merged

Table 24. (cont'd)

Year and Reference	Cyclohexanone (c)									Isophorone	Methyl-cyclohexanone
	Allied Chemical Corp.	Celanese Corp.	Dow Badische Co.	E.I. Dupont Co.	El Paso Natural Gas	Monsanto Co.	Mipro, Inc.	Rohm & Haas Co.	Union Carbide Corp.	Union Carbide Corp.	Frank Enterprises
S.R.I., 1975	C&M	C	C		C	C	C&M	C	C	X	X
S.R.I., 1974	C&M	C	C&M		C	C	C&M	C	C	X	
U.S.I.T.C. Annual a											
1973	X	X	X	X		X	X				
1972	X	X	X	X		X	X				
1971	X	X	X	X		X	X				
1970	X	X	X	X		X	X				
1969	X	X	X	X		X	X				
1968	X	X	X	X		X					
1967	X		X	X		X					
1966	X		X	X		X					
1965											

(c) C - Captive use; M - Merchant sales

Table 24. (cont'd)

Year and Reference	Benzophenone										Acetophenone					
	Aceto Chemical Co., Inc.	GAF Corp.	Givaudan Corp.	Neville-Synthese Organics, Inc.	Norda Inc.	Orbica Products	Parke, Davis Co.	Universal Oil Products	Inmont	Interchemical	Allied Chemical Corp.	Clark Chemical Corp.	Givaudan Corp.	Skelly Oil Co.	Union Carbide Corp.	**Universal Oil Products**
S.R.I., 1975	X	X			X	X	X	X			X	X	X	X	X	X
S.R.I., 1974	X	X	X	X	X	X	X	X			X	X	X	X	X	X
U.S.I.T.C. Annual a																
1973	X				X		X	X			X	X		X	X	
1972	X	X			X		X	X			X	X		X	X	
1971	X	X			X		X	X			X	X		X	X	
1970	X	X			X		X	X			X			X	X	
1969	X	X			X		X				X			X	X	
1968	X	X			X		X	X	X		X			X	X	
1967	X	X			X		X	X			X			X	X	X
1966	X	X			X			X		X	X				X	
1965	X	X			X			X		X	X				X	

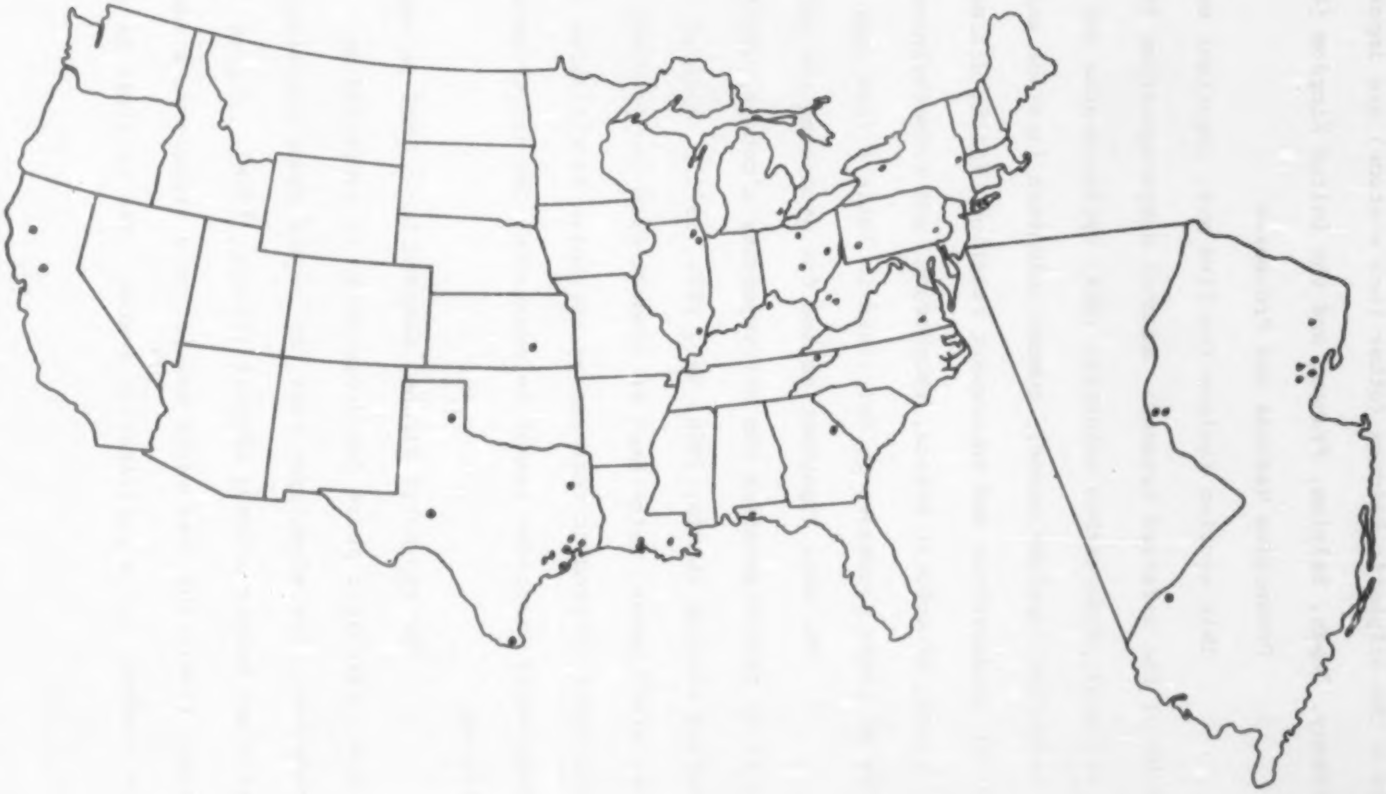

Figure 6. Major Production Sites for the Selected Ketones (From SRI, 1974, 1975)

Major ketone distributors are listed in Table 25. Countries from which the aliphatic ketones (other than acetone) are imported include West Germany, Japan, Belgium, France, and the United Kingdom (USTC, 1971).

3. Production Methods and Processes

This section reviews the five most important methods used in production of the selected ketones: alcohol dehydrogenation (MEK and other linear ketones); hydrocarbon oxidation (MEK, cyclohexanone and acetophenone); phenol reduction (cyclohexanone); cumene oxidation (acetone and acetophenone); and acetone condensation and subsequent reactions (MIBK, diacetone alcohol, mesityl oxide, diisobutyl ketone, isophorone, and trimethylnonanone). The chemistry of these processes is described in Table 8 (see page 19).

The most important method for producing the straight chain ketones is by dehydrogenating the corresponding alcohols, which are obtained by hydrating olefins (Lurie, 1966; SRI, 1974, 1975). Alcohol oxidation processes yield water, which must be removed from the product. Since, at best, the water by-product requires an expensive distillation and, at worst, the ketone-water azeotrope cannot be separated, the dehydrogenation process is preferred.

The sec-butyl alcohol dehydration to MEK is representative. In the U.S., the vapor phase dehydrogenation is preferred over the liquid phase reaction. Its advantages over the liquid phase processes are higher conversion and better process control (Sittig, 1968). Figure 7 describes the process flow. The components consist of a preheater, a vapor phase reaction chamber, and a purification system. The catalyst is a supported

Table 25. Major Distributors of the Selected Ketones (From CMR, 1975f)

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DIETHYL KETONE

Aceto Chemical Co., Inc.
Conray Products Co.
Hexagon Laboratories, Inc.
Roehr Chemical Division

DIISOBUTYL KETONE

Amsco Division Union Oil
Ashland Chemical Co., Industrial Chemicals & Solvents Division
CPS Chemical Co.
Chemisphere Corp.
Dynamic Chemical Products, Inc.
Eastman Chemical Products, Inc.
McKesson Chemical Co.
Stinnes Oil & Chemical Co.
Suburban Chemical Co.
Transworld Chemicals, Inc.
Union Carbide Corp.

METHYL ETHYL KETONE

A.I.D. Chemical Co., Inc.
Allied Chemical Corp., Specialty Chemical Division
Amore Chemicals, Inc.
Amsco Division Union Oil
Amsco Solvents & Chemicals Co.
Arco Chemical Co.
Ashland Chemical Co., Industrial Chemicals & Solvents
Atlanta Chemical Co., Inc.
Buffalo Solvents & Chemicals Corp.
CPS Chemical Co.
Celanese Chemical Co.
Chemisphere Corp.
Chemsol Corp.
Corco Chemical Corp.
DeMert & Dougherty, Inc.
Dixie Chemical Co.
Dynamic Chemical Products, Inc.
Eastman Chemical Products, Inc.
Exxon Chemical Co., U.S.A.
FBC Corp.
Fallek Chemical Corp.
Fish Chemical & Equipment, Inc.
Gage Products Co.
Hoosier Solvents & Chemicals Corp.
Howe & French
IPS Chemicals, Inc.
International Chemical Corp.
Intsel Corp.
Koch International Trading Co., Inc.
Legion Export & Import Co., Inc.

Mallinckrodt Chemical Works
McKesson Chemical Co.
Metro Oil & Chemical Corp.
Morgan Chemicals, Inc.
Mutchler Chemical Co., Inc.
Ochoa Industrial Sales Corp.
Philipp Brothers Chemicals, Inc.
Phipps Products Corp.
Pyramid Chemical Sales Co.
Riches-Nelson, Inc.
SRS, Inc.
Shell Chemical Co.
Stanalchem, Inc.
Suburban Chemical Co.
Tag Chemicals Co.
Tar Residuals Inc.
Texaco Inc., Petrochemical Dept.
Texas Solvents & Chemicals Co.
Thompson-Hayward Chemical Co.
Tobey Chemical Co.
Transworld Chemicals, Inc.
Union Carbide Corp., Chemicals and Plastics

METHYL ISOPROPYL KETONE

Aceto Chemical Co., Inc.
Henley & Co., Inc.
Orlex Chemical Corp.

METHYL n-BUTYL KETONE

Eastman Chemical Products, Inc.
Ohio Solvents & Chemicals Co.
Southchem, Inc.
Southland Solvents & Chemical Co.

METHYL ISOBUTYL KETONE

A.I.D. Chemical Co., Inc.
Allegheny Solvents & Chemicals Co.
Amore Chemicals, Inc.
Amsco Division Union Oil
Amsco Solvents & Chemicals Co.
Ashland Chemical Co., Industrial Chemicals & Solvents Division
Buffalo Solvents & Chemicals Corp.
CPS Chemical Co.
Chemisphere Corp.
Corco Chemical Corp.
Dynamic Chemical Products, Inc.
Eastman Chemical Products, Inc.
Exxon Chemical Co., U.S.A.
Fallek Chemical Corp.
Gage Products Co.
Hoosier Solvents & Chemicals Corp.

Howe & French
International Chemical Corp.
Intsel Corp.
Mallinckrodt Chemical Works
McKesson Chemical Co.
Morgan Chemicals, Inc.
Philipp Brothers Chemicals, Inc.
Riches-Nelson, Inc.
SRS, Inc.
Shell Chemical Co.
Stanalchem, Inc.
Stinnes Oil & Chemical Co.
Suburban Chemical Co.
Tar Residuals, Inc.
Texas Solvents & Chemicals Co.
Thompson-Hayward Chemical Co.
Transworld Chemicals, Inc.
Union Carbide Corp., Chemicals and Plastics

METHYL ISOAMYL KETONE

Amsco Division Union Oil
Ashland Chemical Co., Industrial Chemicals & Solvents Division
Eastman Chemical Products, Inc.
McKesson Chemical Co.
Suburban Chemical Co.
Thompson-Hayward Chemical Co.
Transworld Chemicals, Inc.
Union Carbide Corp., Chemicals and Plastics

METHYL n-HEXYL KETONE

Givaudan Corp.

MESITYL OXIDE

A.I.D. Chemical Co., Inc.
Exxon Chemical Co., U.S.A.
Shell Chemical Co.

DIACETONE ALCOHOL

Aceto Chemical Co., Inc.
Amsco Division Union Oil
Ashland Chemical Co., Industrial Chemicals & Solvents Division
Celanese Chemical Co.
McKesson Chemical Co.
Shell Chemical Co.
Suburban Chemical Co.
Transworld Chemicals, Inc.
Union Carbide Corp., Chemicals and Plastics

Table 25. (cont'd) Major Distributors of the Selected Ketones

CYCLOHEXANONE

A.I.D. Chemical Co., Inc.
Allegheny Solvents & Chemicals Co.
Allied Chemical Corp., Plastics Division
Amsco Division Union Oil
Amsco Solvents & Chemicals Co.
Ashland Chemical Co., Industrial Chemicals & Solvents Division
Atlanta Chemical Co., Inc.
Celanese Chemical Co.
Chemisphere Corp.
Columbia Nitrogen Corp./Nipro, Inc.
Delta Solvents & Chemicals Co.
Dynamic Chemical Products, Inc.
Fallek Chemical Corp.
Hoosier Solvents & Chemicals Corp.
Howe & French
McKesson Chemical Co.
Ohio Solvents & Chemicals Co.
Philipp Brothers Chemicals, Inc.
Stanalchem, Inc.
Suburban Chemical Co.
Tobey Chemical Co.
Transworld Chemicals, Inc.

ISOPHORONE

Aceto Chemical Co., Inc.
Amsco Division Union Oil
Ashland Chemical Co., Industrial Chemicals and Solvents Division
CPS Chemical Co.
Exxon Chemical Co., U.S.A.
International Chemical Co.
McKesson Chemical Co.
Ohio Solvents & Chemicals Co.
Stinnes Oil & Chemical Co.
Suburban Chemical Co.
Thompson-Hayward Chemical Co.
Union Carbide Corp., Chemicals and Plastics

ACETYLACETONE

Aceto Chemical Co., Inc.
Howard Hall & Co.
Henley & Co., Inc.
Lonza Inc.
MacKenzie Chemical Works, Inc.
Westco Chemicals, Inc.

ACETONYLACETONE

Aceto Chemical Co., Inc.
Arsynco, Inc.
Research Organic/Inorganic Chemical Corp.

ACETOPHENONE

Allied Chemical Corp., Plastics Division
Chemical Dynamics Corp.
Clark Chemical Corp.
Givaudan Corp.
Trueger Chemical Co.
Union Carbide Corp., Chemicals and Plastics

BENZOPHENONE

Conray Products Co.
Fabtex Corp.
Givaudan Corp.
ICD Chemicals, Inc.
Norda, Inc.
Orbis Products Corp.
Parke, Davis & Co., Chemical Marketing
Universal Oil Products Co., Chemical Division

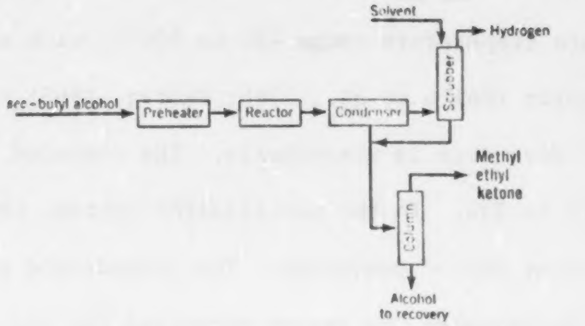

Solvent
Hydrogen
sec-butyl alcohol
Preheater
Reactor
Condenser
Scrubber
Methyl ethyl ketone
Column
Alcohol to recovery

Figure 7. Methyl Ethyl Ketone From Secondary Butyl Alcohol By Dehydrogenation (From Faith et al., 1965)

(Reprinted with permission from Interscience Publishers)

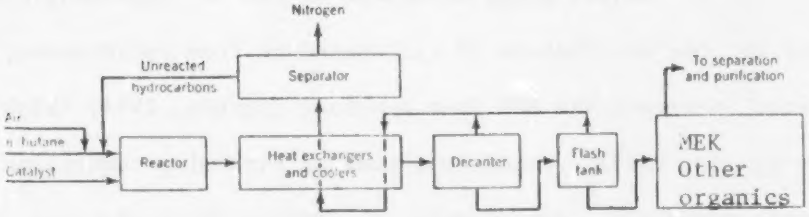

Nitrogen
Unreacted hydrocarbons
Separator
To separation and purification
Air
n-butane
Catalyst
Reactor
Heat exchangers and coolers
Decanter
Flash tank
MEK
Other organics

Figure 8. Methyl Ethyl Ketone From Butane by Liquid-Phase Oxidation (From Faith et al., 1965)

(Reprinted with permission from Interscience Publishers) metal oxide, usually zinc oxide, although other catalysts, such as magnesium oxide, copper oxide, beryllium oxide and chromium oxide have been used (Austin, 1974; Faith et al., 1965). The preferred reaction conditions are the approximate temperature range 400 to 500°C, with a mean residence time of 2 to 8 seconds (Faith et al., 1965; Sittig, 1968; Austin, 1974). Operating pressures are described as atmospheric. The reported alcohol conversion to MEK is from 75 to 85%. In the purification system, the reactor vapors are cooled in a brine cooled condenser. The uncondensed gases are scrubbed, usually with sec-butanol, to remove entrained MEK and sec-butanol; the latter is then recycled. The condensed fraction is distilled and fractionated (Austin, 1974; Sittig, 1968; Faith et al., 1965).

A liquid phase dehydrogenation is reportedly used for MEK production in Europe. The conditions are 300°F at atmospheric pressure using Raney nickel or copper chromite as catalyst. MEK and hydrogen are driven off as soon as they form (Austin, 1974; Faith et al., 1965).

Liquid phase oxidation of the corresponding hydrocarbons can be used for the manufacture of cyclohexanone from cyclohexane; acetophenone from ethyl benzene; and MEK from n-butane (Austin, 1974; Faith et al., 1965; Dorsky et al., 1963). Conditions must be carefully controlled to prevent competing reactions. For example, by varying the conditions, acetic acid can be the major product in butane oxidation (Faith et al., 1965). The cyclohexane and butane oxidations are similar. Figure 8 outlines the process flow chart for the liquid phase butane oxidation. The hydrocarbon is oxidized at ca. 125°C in a solution containing a cobalt or manganese salt as catalyst. Glacial acetic acid and water have been reported as solvents (Dorsky et al., 1963; Faith et al., 1965). With either solvent, an acid resistant reactor must be used. The pressure is generally maintained at about 30 psig in order to keep the hydrocarbon in solution (Dorsky et al., 1963; Faith et al., 1965). Reaction time is reported as 1.5 hours (Dorsky et al., 1963).

Hydrogenation of phenol in a heterogeneous process is the major method for cyclohexanone production. Phenol reduction can be performed either in liquid or gas phase. Figure 9 shows the typical process flow. The reactor temperature is held at 75° to 150°C. While at the lower temperatures phenol conversion is low, at higher temperatures selectivity is poor. The catalyst is either palladium, or some other metal of the palladium group, dispersed on an inert support (1 to 10% by weight). The solid catalyst is usually held within perforated tubes at the bottom of the hydrogenator. The gas consists of hydrogen and nitrogen, generally in a ratio of 85/15 at 15 to 75 psig. Conversion of almost 96% and a yield of almost 95% is reported (Sittig, 1968).

The cumene hydroperoxide process yields phenol, acetone (0.6 pounds per pound of phenol produced) and acetophenone (0.05 pounds per pound of phenol produced) (Lederman and Poffenberger, 1968; Dorsky et al., 1963). The process flow is shown in Figure 10. An emulsified solution of cumene in aqueous sodium carbonate (pH 8.5 to 10.5) and air is fed into a reactor maintained at 160 to 260°F at a pressure slightly above atmospheric. About 30% conversion to cumene hydroperoxide [$C_6H_5C(CH_3)_2O_2H$] is reached after three to four hours. Unreacted cumene is removed by steam or vacuum stripping. The remaining cumene hydroperoxide (approximately 80% concentration) is fed to dilute acid (usually 5 to 25% sulfuric acid at 120-150°F). The resulting mixture is phase separated. The oil layer contains acetophenone and α-methyl styrene in addition to phenol,

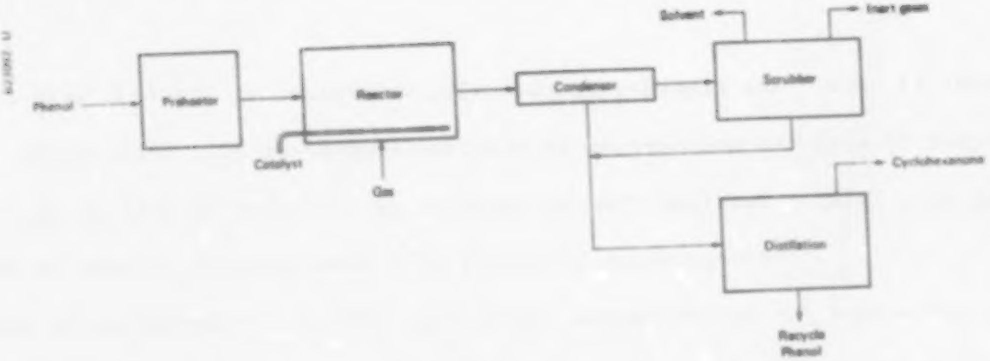

Phenol
Preheater
Reactor
Catalyst
Gas
Condenser
Solvent
Scrubber
Inert gases
Cyclohexanone
Distillation
Recycle Phenol

Figure 9. Cyclohexanone By The Catalytic Hydrogenation of Phenol (From Sittig, 1968)

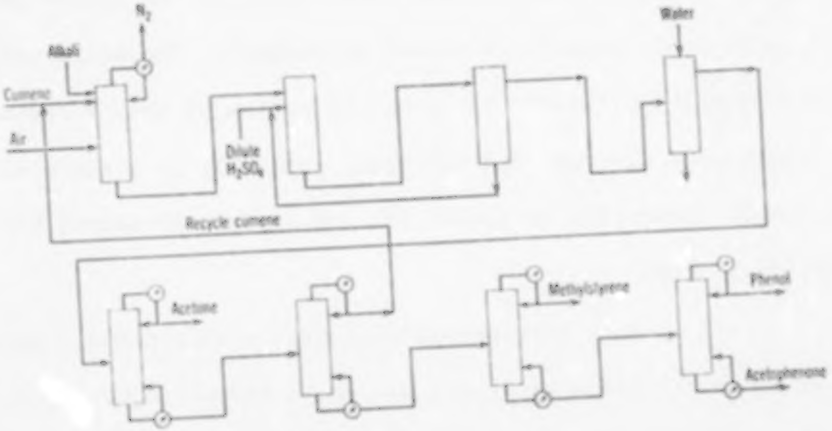

N_2
Alkali
Cumene
Air
Dilute H_2SO_4
Water
Recycle cumene
Acetone
Methylstyrene
Phenol
Acetophenone

Figure 10. Acetone and Acetophenone By Cumene Oxidation (From Lederman and Poffenberger, 1968) (Reprinted with permission from Interscience Publishers)

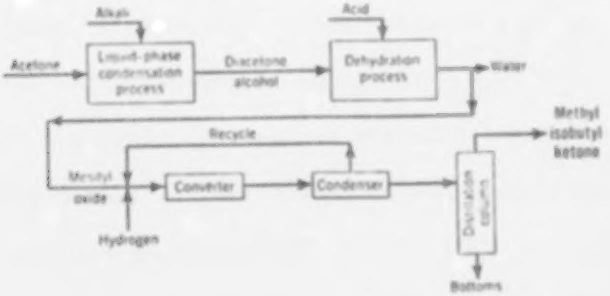

Alkali
Acid
Acetone
Liquid-phase condensation process
Diacetone alcohol
Dehydration process
Water
Recycle
Methyl isobutyl ketone
Mesityl oxide
Converter
Condenser
Distillation column
Hydrogen
Bottoms

Figure 11. Methyl Isobutyl Ketone From Acetone (Via Diacetone Alcohol and Mesityl Oxide) (From Faith et al., 1965) (Reprinted with permission from Interscience Publishers)

acetone and unreacted cumene. These organics are separated by distillation (Lederman and Poffenberger, 1968).

MIBK is the most important ketone produced by acetone condensation. The flow sheet for its preparation and that of its intermediates, diacetone alcohol and mesityl oxide, is shown in Figure 11. Acetone is dimerized to diacetone alcohol by a liquid phase reaction at 0 to 20°C over a fixed bed, alkaline catalyst (Austin, 1974; Faith _et al._, 1963). Reaction times of approximately 6 seconds are reported for a tubular reactor operation (Sittig, 1968). Diacetone alcohol is then dehydrated in the presence of a weak acid at 100 to 120°C to mesityl oxide. The mesityl oxide is then hydrogenated at mild temperatures (120 to 165°C) over nickel or copper catalyst (Austin, 1974; Faith _et al._, 1965; Sittig, 1968).

Isophorone and diisobutyl ketone are products of triacetone alcohol. The acetone trimer is a by-product in the diacetone alcohol production (Oosterhof, 1967), or under modified reaction conditions it is obtained as the major product (Lurie, 1966; Sittig, 1968).

4. Market Prices

Table 26 reports ketone prices for the years 1970-1975. The price of MEK has been steadily decreasing since 1958. Its price per pound has decreased as follows: 12.5¢ from 1958 to 1967; 11.5¢ from 1968 to 1969; 10.5¢ in 1970; 10¢ in 1971; and 8¢ in 1973 (SRI, 1972b; CMR, 1974a). Since 1958, MIBK price has remained constant in the range of 13.0 to 14.5¢ per pound (SRI, 1972b). The methyl isoamyl ketone price has remained constant at 17.5¢ per pound from 1962 to 1972 (SRI, 1972b). The cyclohexanone price has widely fluctuated in the period 1954 to 1975.

Table 26. Market Prices of Selected Ketones

	Price in Dollars per Pound									
	1970 (a)	1971 (a)	1972 (a)	1973 (a)	1974 (b)			1975 (c)		
					Low	——	High	Low	——	High
Acetone, unit value	0.04	0.04	0.04	0.04						
Acetone, f.o.b. plant					0.14		0.16	0.14		0.16
Acetophenone, unit value			0.10	0.28						
Acetophenone, tank f.o.b. plant						0.40			0.40	
Benzophenone, unit value	1.11	0.99	1.36	1.39						
Benzophenone, 200 lb. drums					1.50		1.50		2.20	
Cyclohexanone, unit value	0.11	0.11	0.12	0.14						
Cyclohexanone, tech., tank					0.36		0.39	0.36		0.39
Diacetone alcohol, unit value	0.13	0.12	0.12	0.12						
Diacetone alcohol, acetone free, tank dlvd.					0.22		0.225	0.225		0.23
Diisobutyl ketone (isovalerone), tank dlvd.									0.245	
Ethyl amyl ketone, tank dlvd.						0.38			0.36	
Ethyl butyl ketone, tech., truckload drums									2.52	
Isophorone, tank dlvd.						0.30			0.30	
Methyl isoamyl ketone, tank dlvd.	0.175 (d)	0.175 (d)	0.175 (d)		0.18		0.23		0.23	
Methyl n-butyl ketone, tank dlvd.						0.225			0.28	
Methyl isobutyl ketone, unit value	0.12	0.11	0.11	0.11						
Methyl isobutyl ketone, tank dlvd.	0.135 (d)	0.135 (d)	0.135 (d)		0.20		0.25	0.23		0.25
Methyl ethyl ketone, unit value	0.09	0.08	0.08	0.08						
Methyl ethyl ketone, tank dlvd.	0.105 (d)	0.10 (d)	0.10 (d)			0.18			0.18 (e)	
Mesityl oxide, tank dlvd.						0.20		0.20		0.23

(a) USITC, Annual a
(b) CMR, 1974c
(c) CMR, 1975e
(d) SRI, 1972b
(e) East Coast

According to the Chemical Economics Handbook (SRI, 1973), cyclohexanone price was 31¢ per pound (delivered) from 1959 to 1967, but it was reduced in 1968 to 18¢ per pound (delivered) in order to compete with isophorone as a coating solvent. Since growth was less than expected, the price was increased in May 1973 to 19.5¢ per pound (SRI, 1973). The Chemical Marketing Reporter (1974c, 1975e) reported that the price in 1974 and 1975 ranged from 36 to 39¢ per pound, delivered.

5. Market Trends

a. Methyl Ethyl Ketone

Although MEK recently lost a thirty million pound market with the closing of the Mobil Oil Co.'s terephthalic acid plant (see Discontinued Uses, page 85), other major market outlets are expected to remain fairly steady. The coatings industry is expected to dominate future trends. The Chemical Marketing Reporter (1975a) expects overall demand to increase at 4% in comparison to a historical growth of 6.5% (1963 to 1973). Demand is expected to reach 622 million pounds in 1978. Feedstocks are, however, expected to be tight in the near future.

Demand for MEK in the coatings industry is chiefly influenced by expansion of the coatings market, by environmental and occupational health regulations and by technological developments. Although solvent based coatings constitute 65% of all chemical coatings (see Major Uses, pages 69-82), they are losing part of their share to new technologies which require reduced solvent content or no solvent at all (Kline, 1975).

Historically, the major regulatory influence has been the spread of air pollution regulations based on Los Angeles Rule 66, which restricts branched chain ketones like MIBK to a greater extent than MEK and other straight chain ketones. The coatings market has met the regulatory action by removing branched chain ketones and reformulating with straight chain ketones, reformulating with other solvent systems, and moving toward newer technologies. The overall historical effect has been moderate growth for MEK (Kline, 1975; SRI, 1972a; CMR, 1975a).

The Occupational Safety and Health Administration (OSHA) has recently initiated new occupational standards for MEK and six other ketones: methyl n-propyl ketone; methyl n-hexyl ketone, ethyl n-butyl ketone; MIBK; cyclohexanone; and mesityl oxide (Anon. 1975c, 1975e, 1975f). The new standards set an "action level" at one-half the maximum permissible exposure limit. The provisions of the occupational standards are discussed in "Regulations" (pages 286-287). These standards, if they come into effect, could weaken the market position for MEK, as well as the other solvents presently exempt from some air pollution controls. It also might result in further weakening of the solvent based coatings share of the coating market.

The occupational health problems in vinyl chloride plants might create some losses in PVC resin manufacture (Anon., 1975d). Since formulation of PVC coatings is an important outlet for MEK as well as other ketones (see Major Uses, pages 72-80), reduction in PVC resin manufacture could in turn weaken the MEK market demand. However, if the PVC market is replaced by other resins that use ketones, the net effect for MEK would not be significant.

Goldstein (1975) has suggested that increased costs in petroleum feedstock might improve the market position of cellulosic products.

If this prediction is accurate, it represents a positive influence in the MEK market. MEK as well as other ketones are common solvents for cellulosics (see Major Uses, pages 72-80).

b. Methyl Isobutyl Ketone

The demand for branched chain ketones, including MIBK, is declining as the result of air pollution regulations based on Los Angeles Rule 66 (Oosterhof, 1967; CMR, 1975a). The Chemical Marketing Reporter (1975a) stated that while MIBK production is on the decline, the sales have not been drastically reduced. Historical demand for MIBK (1963 to 1973) has dropped at 1% per year. The Chemical Marketing Reporter (1975a) has projected decline through 1975 at 5% per year; 125 million pounds in 1979 down from 161 million pounds in 1975.

c. Cyclohexanone

The nylon market accounts for some 95% of the cyclohexanone produced (SRI, 1973). The currently expanding nylon market is reportedly straining feedstock capacity (Greek, 1975). At currently predicted expansion, demand is expected to exceed existing and proposed feedstock capacity by 1977.

About 5% of the cyclohexanone produced is used as a solvent. Since it is exempt from restrictions on photochemically active solvents, it has been used as a replacement for restricted solvents, such as isophorone. However, the Chemical Economics Handbook (SRI, 1973) reported that its growth in the solvent market was less than expected. According to the Chemical Economics Handbook, the reasons for the slower market growth included slower than expected promulgation of the Los Angeles

Rule 66 type air pollution regulations in the areas with a high demand for cyclic ketones and increased recycling capabilities in the coating plants. The recent OSHA decision placing cyclohexanone under "action level" standards could weaken its present strength as a replacement for the photochemically reactive solvents. This, along with the expected, tight supply could reduce cyclohexanone's share of the coating solvent market.

d. Other Ketones

While branched chain ketones have been losing strength in the solvent market, straight chain ketones have in general been gaining (CMR, 1974a, 1975a). The straight chain ketones have been used to replace both branched chain ketones and other photochemically reactive solvents (CMR, 1974a, 1975a; Levy, 1973). However, methyl n-butyl ketone failed to be a suitable substitute for MIBK since it was found to cause nerve damage (CMR, 1975a) (see p. 261). Demand for acetophenone in solvent systems and for other uses is not expected to appreciably change (CMR, 1975b).

B. Uses

1. Major Uses

Table 27 lists the major uses of the selected ketones. Table 28 summarizes estimates of consumption in 1973 for MEK, MIBK, and cyclohexanone. Some elucidation is also given for the uses of diacetone alcohol, mesityl oxide, isophorone, acetophenone, and benzophenone. Consumption of the eight ketones totaled approximately 1.5 billion pounds. Only qualitative information is available on the consumption of the remaining ketones. But the literature does suggest that large proportions of diacetone alcohol, isophorone and mesityl oxide are consumed as solvents (USTC, 1971). It also appears that non-solvent uses consume most of the acetophenone and benzophenone production (Browning, 1965; Dorsky et al., 1963; Anon., 1975a; van den Dool, 1964).

a. Chemical Intermediates

The cyclohexanone used as a chemical intermediate accounts for approximately 95% of its total production. The products, adipic acid and ε-caprolactam, are used in the manufacture of nylon 66 and nylon 6, respectively (SRI, 1973; Kralovec and Louderback, 1965).

Synthesis of the peroxide and the oxime of MEK accounted for approximately 1% of consumption (USTC, 1969, 1971). While the oxime is used as an anti-skimming agent in surface coatings (USTC, 1971), the peroxide is important as a radical polymerization initiator (USTC, 1969; Noble, 1974).

b. Solvents

Solvents can be divided into two rather broad areas: those used in coatings and allied formulations (inks, adhesives, etc.) and those used for selective extraction. For use in coatings, the solvent must

Table 27. Major Uses of the Selected Ketones

Use	Ketones	References
Application solvent:		
Coatings Cellulosic, vinylic and acrylic resins	All aliphatic ketones and acetophenone	Hagemeyer, 1952 Lurie, 1966 Browning, 1965 USTC, 1971 Dorsky, 1963 Dean, 1968, 1972a, 1972c
Coatings Alkyd, epoxy and other natural and synthetic resins	All aliphatic ketones and acetophenone	Dean, 1970, 1972b Blount, 1975 Lurie, 1966
Adhesives	MEK, MIBK	Blomquist, 1963
Selective extraction:		
Lube oil/wax refining	MEK, MIBK, diisobutyl ketone	Tuttle, 1968 Lurie, 1966
Rare metal refining	MIBK, diisobutyl ketone, mesityl oxide	Seaborg, 1963 Nielsen, 1966 Taylor, 1969 Silvernail and McCoy, 1969
Chemical intermediate:		
Product ε-caprolactam Adipic acid	Cyclohexanone	SRI, 1973 Kralovec and Louderback, 1965
Methyl ethyl ketoxime	MEK	USTC, 1971
Methyl ethyl peroxide	MEK	USTC, 1969

Table 28. Estimated Consumption of Selected Ketones in 1973 (From SRI, 1973 and CMR, 1974a, 1975a)

Ketone	Ketone Produced in 1973		Ketone Consumed in 1973 in Thousands of Pounds (d)						
			Solvent						Chemical Intermediate and Other Uses
			Coatings				Adhesives	Extraction	
	In Thousands of Pounds	Percent of Total Ketone	Vinylic	Acrylic	Cellulosic	Not Specified			
Methyl ethyl ketone	540,709 (a)	37.6	183,841 (34%)	64,885 (12%)	75,699 (14%)	37,850 (7%)	75,699 (14%)	37,850 (7%) (e)	64,885 (12%) (g)
Methyl isobutyl ketone	154,751 (a)	10.8				100,764 (65%)	Included in "other uses"	9,285 (6%) (f)	24,760 (16%) (g,h)
Diacetone alcohol	50,994 (b)	3.5	Major						May be large
Isophorone	28,000 (c)	1.9	Major						Minor
Mesityl oxide	22,000 (c)	1.5	Major						Minor
Subtotal	796,454	55.3							
Cyclohexanone	638,156 (a) [45,937 (b)]	44.4	31,908 (5%)						606,248 (95%)
Acetophenone	2,246 (a)	0.2	Some						Major
Benzophenone	741 (a)	0.1	Minor						Major
Total	1,437,597	100.0							

(a) Production data, see Table 20.
(b) Sales data, see Table 20.
(c) Estimated, see Table 22.
(d) Percentages based on total of each ketone.
(e) For lube oil dewaxing only.
(f) For rare metal refining only.
(g) Unspecified, might include some solvent use.
(h) 13% of methyl isobutyl ketone is exported.

dissolve or disperse a material into a form suitable for application, and after application the solvent must evaporate. Primary consumption of the ketonic solvents occurs through their use in the coatings industry. In selective extractions, the solvent dissolves a substrate from a mixture in order to separate and purify one or more of the components. Ketones are consumed in moderate quantities for extraction purposes, e.g. for rare metal refining and for lube oil/wax refining (Wyart and Dante, 1969; von Fisher and Bobalek, 1964; Tuttle, 1968).

c. Coating Formulations

Surface coatings are applied to impart protection, special properties and decoration. Coatings consist of films formed from natural or synthetic resins, which are usually combined with pigments and other additives to control drying or provide special qualities. Solvents are used to prepare a form in which the coating can be suitably applied. The solvent must disperse the coating materials and yield a solution with a viscosity suitable for application. After application, it must evaporate at a rate capable of yielding the correct finish (SRI, 1971; Donnel, 1967; Higgins, 1964; von Fisher and Bobalek, 1964; and Friedberg, 1965). The ketones are particularly good solvents for coating formulations. They have greater solvent strength than other oxygenated solvents of similar boiling points, and they have the required viscosity characteristics. Because they have excellent capacity for being diluted with the relatively cheap hydrocarbon solvents, they have an important economic advantage over other classes of active solvents, such as the esters (Martens, 1968; Wyart and Dante, 1969).

The ketones are generally recognized as especially good solvents for vinylic, cellulosic and acrylic resins (Lurie, 1966; USTC, 1971; Klug, 1964; Donnel, 1967). Ketones generally comprise about 25% of the total weight of coating formulations (see Table 29). The active solvent concentration can go as high as 40% in some formulations (von Fisher and Bobalek, 1964). While coatings for spray application are formulated with the low boiling, low molecular weight ketones, brush application requires formulation with the higher boiling, higher molecular weight, and more expensive ketones (Martens, 1968). Ketones have also been mentioned as solvents for alkyd, epoxy, and other resins (Blount, 1975; Hughes et al., 1975).

While the coatings industry consumed an estimated 800 million pounds of ketones worth 70 million dollars in 1970, oxygenated solvent consumption was estimated at 1850 million pounds (valued at 185 million dollars) (SRI, 1971). Estimates of acetone consumed as a coating solvent ranged from 200 to 350 million pounds (USTC, 1971; CMR, 1974b; Blackford, 1975). It is concluded that acetone and MEK account for roughly two-thirds of the ketones consumed and MIBK about one-sixth. The bulk of the remaining ketonic solvents consists of cyclohexanone, mesityl oxide, isophorone and diacetone alcohol, which were consumed in more or less similar quantities (see Table 22, page 46 and Table 28).

Hughes et al. (1975) have published a conflicting estimate of solvent consumption by the paint industry for 1972. While their dollar estimate is not significantly different, their estimated quantities are lower: total solvent, 2930 million pounds; oxygenated solvents, 930 million pounds; and ketones, 350 million pounds. The ketones used were estimated as follows (in millions of pounds): acetone, 136; MEK, 145; MIBK, 60; and all other ketones, 11.

Table 29. Composition of a Typical Coating Formulation:
White Vinyl Aircraft Enamel
(From Gaynes *et al.*, 1967)

Material	Percentage by weight
Film formers	
Titanium dioxide	16.8
Santicizer 160	3.0
Amberlack 292X	41.7
VAGH	7.7
Guaiacol	<0.1
RRZ (Vanderbilt)	0.6
Total	69.9
Solvents	
Cyclohexanone	1.5
Isophorone	4.9
Methyl isobutyl ketone	19.1
Toluol	4.6
Total Solvent	30.1

The end use of ketonic solvents in coatings can only be qualitatively estimated from resin consumption data. Surface coating data for 1970 is listed in Table 30. The criteria for industrial use is that the

Table 30. Consumption of Surface Coatings in 1970
(From SRI, 1971)

	Millions of gallons	Value in millions of dollars
Total Surface Coatings	820	2,760
Trade Sales	425	1,530
House	380	1,360
Water based	230	755
Solvent based	150	605
Miscellaneous	45	170
Automotive refinishing	20	110
Traffic paint	15	30
Other	10	30
Industrial	395	1,230
Automotive	40	130
Wood furniture and fixtures	50	110
Metal containers	40	110
Metal furniture and fixtures	25	85
Appliances	20	80
Machinery and equipment	25	75
Paper film and foil	25	75
Sheet, strip and coil	15	65
Factory finished wood	15	45
Transportation (non-automotive)	15	45
Electrical insulation	10	40
Other	50	150
Maintenance finishes	65	225
Exterior	35	125
Interior	20	65
Marine	10	35

coating was applied in a factory (SRI, 1971, von Fisher and Bobalek, 1964). Consumption in automobile refinishing plants, which apply coatings just as in manufacturing plants, is classified as trade sales. Although trade sales accounted for somewhat more than one-half of the total coatings market, it is estimated that they consumed only a relatively small percentage of the ketones. Of the total 425 million gallons of trade sales paint, 230 million gallons were water-based house paints, which were not formulated with ketones (Dean, 1972a, 1972b; Donnel, 1967). The remaining trade sale paints consisted of 150 million gallons of solvent-based house paint and 45 million gallons of miscellaneous paints, which consisted mainly of automobile refinishing and traffic paints (SRI, 1971).

Table 31 summarizes trade sales data for alkyd and acrylic coatings. Alkyd coatings are generally thinned with the less expensive hydrocarbon solvent. Some formulations, such as for spray applications, do contain some low boiling ketones to impart quick drying (Dean, 1972b; Donnel, 1967). Since this is not necessary in the house paints, it is concluded that the majority (*ca*. 139 million gallons) of the total solvent-based house paint (*ca*. 150 million gallons) consumed only a small quantity of the ketones. The automobile refinishing and traffic paints, which do require quick drying, will contain some ketone. Overall, it is concluded that ketonic solvents are not heavily consumed in trade sale paints, and that the trade sale paints which most likely contain ketones are predominantly specialty paints and not usually consumer items.

Table 31. Consumption of Selected Surface Coatings in Trade Sales

Alkyd Coatings Consumption in 1971
(from Dean, 1972b)

Type	Amount in millions of gallons
House paint	139
Automobile refinishing paint	12
Traffic paints	10
Miscellaneous paints	4

Solvent Based Acrylic Coatings Consumption in 1971
(from Dean, 1972a)

Type	Amount in millions of gallons
Automobile refinishing paint	6
Other formulations	2

Table 32 describes the industrial consumption of acrylic, cellulosic, and vinylic coatings; these are thought to consume most of the ketones (USTC, 1971; SRI, 1972a). Alkyd coatings, which are sometimes formulated with ketones, are also included. Acrylic coatings are important as automobile top coats and for other metal coatings; cellulosic resins are heavily favored for wood and paper; and vinylic resins are important as metal coatings and also in textile coatings. Altogether, these coatings are fairly evenly divided over the industrial sectors, and it would seem then that ketonic solvents are also fairly evenly divided within the coatings industry.

d. Adhesives

The solvent action in adhesive application is similar to that in coatings. The solvent must disperse the adhesive binder to a spreadable form and must evaporate after application. The binder can consist

Table 32. Consumption of Selected Industrial Surface Coatings

Acrylic Coatings (from Dean, 1972a)

Type	Amount in millions of gallons
Automobile topcoat finishes	18.0
Coil coatings	4.5
Appliance coatings	3.5
Other coatings (a)	7.0
Total	33.0

Cellulosic Coatings (from Dean, 1968)

Type	Amount in millions of gallons
For nitrocellulose and cellulose acetate-butyrate	
Wood furniture finishes	29
Factory finished wood	6
Paper, film and foil	15
Miscellaneous coatings (b)	8
For ethyl cellulose and other cellulose derivatives	5
Total	63

Vinylic Coatings Consumption in 1971 (from Dean, 1972b)

Type	Amount in millions of gallons
PVC resin solution	
Can and closure containers	18
Maintenance and marine	6
Miscellaneous metals (c)	9
Other (d)	7
Total	40

Type of PVC Dispersion	Amount of PVC consumed in millions of pounds
Plastisols in paint-like coatings for metal surfaces	12.5
Organosols in paint-like coatings for metal surfaces	5.5
Other plastisols and organosols (e)	440.0
Total	458.0

(a) Includes metal containers, metal furniture, transportation other than automotive and factory finished wood.

(b) Includes cans, machinery, automotive and metal finishes.

(c) Includes automobiles, appliance equipment and machinery, electric wire and furniture.

(d) Includes film and foil, magnetic tape, paper and wood.

(e) Most used in molding and textile coating.

Table 32. (cont'd)

Acrylic Coatings (from Dean, 1972a)

Type	Coatings (millions of gallons)	
Product Finishes		145
Wood furniture and fixture finishes (f)	40	
Machinery and equipment enamels (g)	22	
Metal furniture finishes	20	
Auto, truck and bus finishes (h)	12	
Metal container finishes (i)	10	
Appliance finishes (j)	5	
Insulating varnishes (k)	3	
Coil, sheet and strip coatings (l)	3	
Prefinished wood primers	3	
Toy, sporting good, gym and baby equipment finishes	2	
Other industrial product finishes (m)		
Maintenance Finishes		35
Exterior coatings	18	
Interior coatings	12	
Marine coatings	5	
Total		180

(f) Includes nitrocellulose lacquers plasticized with alkyd resins.

(g) Includes farm equipment, construction equipment, earth moving equipment, electrical machinery, stationary machinery and machine tools.

(h) Includes auto engine enamels and chassis enamels for buses and trucks.

(i) Includes drum enamels and coatings for the exterior of metal cans.

(j) Includes major and minor appliances plus air conditioning and heating equipment.

(k) For electrical insulation applications (excludes polyester coatings).

(l) All prefinished metal coil coatings are included.

(m) Includes coatings for railroad equipment, aircraft, miscellaneous transportation vehicles, paper and paperboard, flexible packaging materials (such as film and foil), hardware, silk screens, cable, leather, and other miscellaneous applications. Tinting color vehicles are also included.

of natural gum, rubber or synthetic resin. Some of the more important adhesives using ketonic solvents are based on phenol-epoxy resins, phenol-butyral resins and cellulose acetate-butyrate resins, all of which are used for metal bonding. These are used in aircraft dopes, for automotive manufacturing, and joining tubular metal (e.g., bicycles and refrigerator cooling coils). Other systems include rubber-based adhesives used in masking tape and as can sealers and butadiene-acrylonitrile/vinyl chloride systems for leather binding (Blomquist, 1963).

e. Extractive Solvents

From 6 to 10% of the ketonic solvents are consumed in refining rare metals and dewaxing lube oil. The refining processes take advantage of the ketones capability to dissolve or not to dissolve some components of a mixture. The ketones used for lube oil/wax refining include MEK, MIBK, and diisobutyl ketone (USTC, 1971; Tuttle, 1968). Ketones employed for rare metal extraction include 2,4-pentanedione, MIBK, diisobutyl ketone, and mesityl oxide (Lurie, 1966; Browning, 1965; USTC, 1971).

The flow sheet for a typical oil/wax refining operation is shown in Figure 12. In this operation, the feedstock and solvent are heated to approximately 125°F. The ratio of the solvent to feedstock is in the range of 2.2 to 3.2. Since the solvent will selectively dissolve the oil, the wax can be crystallized and collected by a rotary vacuum filter maintained at 17 to 20°F. Oil content of the wax cake is further reduced by washing with cold, oil-lean solvent. Solvent is separated from the processed wax cake and from oil by distillation. In a typical operation, 7500 barrels of heavy paraffin distillate is processed daily with an annual yield of 200 million pounds of wax and one million barrels of lubricating and other oils. Solvent loss in the process is estimated at 0.1% of the feed (Tuttle, 1968; Nelson, 1968; SRI, 1972a).

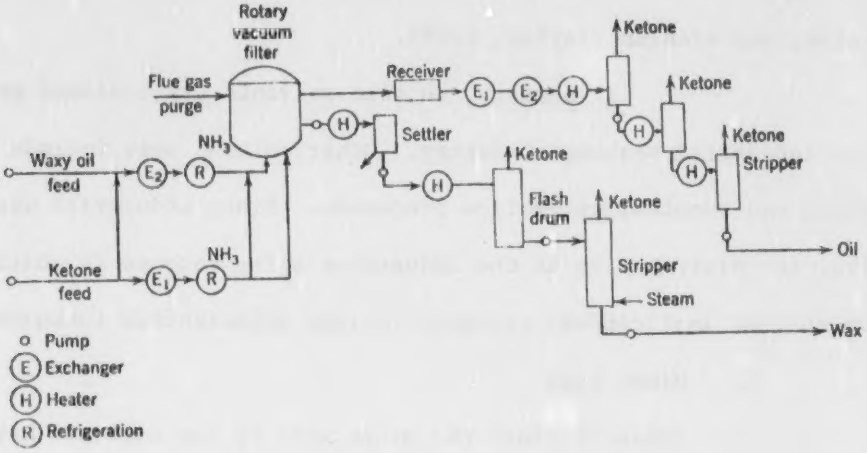

Rotary vacuum filter
Flue gas purge
Receiver
Ketone
Ketone
Ketone
Stripper
Settler
NH3
Waxy oil feed
E2
R
E1
H
Ketone
Flash drum
Ketone
Stripper
Steam
Oil
Wax
Ketone feed
NH3
o Pump
E Exchanger
H Heater
R Refrigeration

Figure 12. Flow Plan For Solvent Dewaxing
(From Tuttle, 1968)
(Reprinted with permission from Interscience Publishers)

Rare metal refining utilizes the partitioning of metal complexes between ketonic and aqueous phases. The process consists of preparing the appropriate metal ion complexes in aqueous solution followed by liquid/liquid extraction with the ketonic solvent. A typical example of this procedure is the separation of tantalum and niobium from ores containing the two metals as well as titanium, zirconium, iron, manganese and other metals. The fluorides of tantalum and niobium can be selectively extracted from the aqueous phase into MIBK. While tantalum will partition into the MIBK at moderate acidity, niobium requires higher acidities. The metals can be isolated either by first extracting tantalum at low pH and then extracting niobium at high pH with fresh solvent, or by extracting both metals at high pH and then partitioning the niobium out of the organic phase with a fresh, low pH aqueous phase (Taylor, 1969).

The ketonic extraction procedure is used for refining the actinides (Seaborg, 1963; Silvernail and McCory, 1969), including actinium, thorium, uranium, plutonium, zirconium, hafnium (Nielsen, 1966), tantalum, and niobium (Taylor, 1969).

In summary, ketonic solvents are consumed primarily in the industrial coatings industry. Other solvent uses include lube oil dewaxing and chemical extraction processes. Since industrial uses are pervasive, the distribution of the industries using ketones in coatings and other solvent applications probably follows urbanization throughout the U.S.

2. Minor Uses

Table 33 lists the minor uses of the selected ketones. Most are either as chemical intermediates or as solvents. Some are closely related to their major uses; their classification as minor uses was based on the relatively small amounts consumed. Minor solvent formulation uses include: inks (MEK, MIBK, methyl isoamyl ketone, mesityl oxide, diacetone alcohol, cyclohexanone, and 2,5-hexanedione); pesticides (MIBK, diacetone alcohol, and cyclohexanone); and wood stains (MEK, MIBK, diisobutyl ketone, diacetone alcohol, and 2,5-hexanedione).

Selective extraction with ketones is used in the pharmaceutical industry, tall oil refining industry, and for the laboratory extraction and analysis of aqueous metals (MIBK, diisobutyl ketone, mesityl oxide). Other minor uses taking advantage of the ketonic solvent power include the cleaning and degreasing of leather, metal, and wool (MEK, MIBK, cyclohexanone, and methylcyclohexanone) and the formulation of paint, varnish, and rust removers (MEK, diacetone alcohol, and mesityl oxide).

Table 33. Minor Uses of Ketones

Ketone	Uses	References
Acetophenone	Intermediate in the syntheses of pharmaceuticals, resins, corrosion inhibitors, rubber chemicals, dyestuffs, and flavor and fragrance materials.	Dorsky *et al.*, 1963 Browning, 1965 Anon., 1975a Opdyke, 1973/74
2,4-Pentanedione	Intermediate in the syntheses of acetylacetone peroxide, other 1,3-diketones, 1,3,5-triketones, pyrroles, pyrazoles, isoxazoles, quinolines.	Lurie, 1966 Ream, 1952
	Preparation of metal chelates for use as driers in coatings.	Freeman, 1964
	Preparation of dental materials.	Freeman, 1964
	Color photography developing.	
	Gasoline additives.	Shell Internationale, 1963
2,5-Hexanedione	Intermediate in the synthesis of perfume ingredients and other materials.	Lurie, 1966 Reynolds, 1952
	Preparation of chelates.	
	Tanning agent.	
	Solvent for inks.	Bruno, 1968
	Solvent for wood stains.	Peacock, 1969
	Gasoline additives.	Shell Internationale, 1963
Benzophenone	Flavor and fragrance ingredient.	Opdyke, 1973/74
	Drier in U.V. inks.	Van den Dool, 1964
Cyclohexanone	Solvent to inks and pesticides.	Bruno, 1968
	For cleaning and degreasing metals and leathers.	Browning, 1965
	In paint removers.	
	As a spotting and relustering agent.	
	Solvent for textile dying.	S.R.I., 1973
	Sludge solvent in oil for piston-type aircraft lubrication.	Kralovec and Louderback, 1965
Diacetone alcohol	Component in castor-oil based hydralic fluids.	USTC, 1971 Lurie, 1966
	Solvent for inks, pesticides and woodstains.	Bruno, 1968 Peacock, 1969
	In paint and rust removers.	Rector, 1952
	As a viscosity index improver for lube oils.	
Diisobutyl ketone	Solvent for extracting pharmaceuticals.	Lurie, 1966 Blackwood, 1969
	Laboratory reagent for analysis of aqueous metals.	Skougstad, 1970
	Solvent for wood stains.	Peacock, 1969
	In rubber for milled crepe rubber.	Browning, 1965
	Intermediate for the syntheses of dyes, inhibitors, pharmaceuticals and insecticides.	
Ethyl amyl ketone	As flavor and fragrance additive.	Opdyke, 1973/74
Ethyl butyl ketone	Intermediate in the synthesis of organic products.	Browning, 1965
Isophorone	In synthesis of 3,5-xylenol.	Leston, 1971
	In synthesis of plant growth retardants.	Haruta, 1974

Table 33. (cont'd)

Ketone	Uses	References
Methylcyclohexanone	In varnish and rust removers.	Browning, 1965
Methyl ethyl ketone	Intermediate in the synthesis of methyl isopropenyl ketone, sec-butylamine, 1,3-diketones. As a solvent for inks and wood stains. In paint removers. As a dye solvent. In degreasing woolens. In manufacture of artificial leathers. As an extractant in hardwood pulping. Laboratory solvent. In pharmaceuticals and cosmetics. Stabilizer for methylene chloride.	Lurie, 1966 Bruno, 1968 Peacock, 1969 Downing, 1967 Hagemeyer, 1952 S.R.I., 1972 Browning, 1965 Beckers, 1975
Methyl isoamyl ketone	Solvent for inks.	Bruno, 1968
Methyl isobutyl ketone	Solvent for pesticides in wood stains and inks. For cleaning and degreasing metals. Intermediate in the synthesis of imidazoles and acetal ethers. Denaturant for ethanol. Extractant for tetracycline salts. Laboratory reagent for the analysis of aqueous metals.	Lurie, 1966 Browning, 1965 Peacock, 1969 Bruno, 1968 Pentz and Lescisin, 1965 Blackwood, 1969 Skougstad, 1970
Methyl *n*-amyl ketone	As a fragrance and flavor ingredient.	Rector, 1952
Mesityl oxide	Solvent for inks. In paint and varnish removers. In stain removers. Synthesis of lube oil additives and plasticizers. As a carburetor cleaner.	Bruno, 1968 Downing, 1967 Lurie, 1966

Several of the ketones are either used as flavor and fragrance materials (methyl n-amyl ketone, methyl n-hexyl ketone, ethyl butyl ketone, ethyl amyl ketone, acetophenone, and benzophenone) or to synthesize such materials (acetophenone, 2,4-pentanedione and 2,5-hexanedione).

3. Discontinued Uses

At the present time, branched chain ketones are declining as solvents for coatings and allied formulations. The decline results from nationwide adoption of air pollution regulations based on Los Angeles Air Pollution Control District's Rule 66. This decline is discussed in more detail in Market Trends (see page 65). Substitution of methyl n-butyl ketone for MIBK as a coating solvent was started but has ceased, since it was found to cause nerve damage (CMR, 1975a).

The use of MEK in the manufacture of terephthalic acid from xylene at the Mobil Chemical Company plant at Beaumont, Texas (Towle et al., 1968; CMR, 1974a) has been discontinued for economic reasons. This market was estimated to consume 41 million pounds of MEK in 1970 (SRI, 1972a), and 30 million pounds in 1973 (CMR, 1974a).

Acetophenone was reportedly used during World War II as an intermediate for styrene production. This manufacturing process is not now competitive (Dorsky et al., 1963). Use of acetophenone as a sedative has ceased because of its narcotic effect (Merck Index, 1952; Browning, 1965).

4. Projected or Proposed Uses

The available literature provided no suggestions for new solvent uses or for replacement of other solvent systems with ketonic systems. The information on replacing branched chain ketones with linear ketones is discussed in Market Trends, p. 65.

The use of cyclohexanones as intermediates in catechol synthesis has been proposed (Anon., 1975b).

5. Possible Alternatives to Use

a. Solvent For Formulating Coatings

Since ketonic solvents are consumed in greatest quantities in formulating industrial coating systems, one possible means of reducing their consumption is to eliminate some non-essential coatings. Industrial coatings are applied to wood, metal, paper, textiles, and other surfaces for protection, decoration, and imparting other useful properties. The coating film will prevent the rusting or corroding of metal surfaces and the rotting of wood. Textile coatings enhance durability and value; they are often used to simulate more expensive materials (Higgins, 1964). Paper coatings also give decoration, durability, and special properties. Coatings provide packaging materials with a barrier against water, oxygen, carbon dioxide, hydrogen sulfide, greases, fats, oils, and miscellaneous chemicals. Some printing methods require that the paper be coated (Whitney _et al_., 1967). It is judged that the vast majority of coating uses could not be eliminated without accepting some economic penalty.

The electroplating of metal surfaces is a possible alternative to surface coatings formed by resin films. Since the process requires that the object being coated conduct a charge, it is limited to metals. Insufficient data was available to compare the cost or durability of the plated and film coatings. Electroplating does create potential occupational health and environmental problems, such as the difficult procedure of removing metal ions from waste-water discharges (Lowenheim, 1965).

Other alternatives include the removal or reduction of solvent used in the coating formulation. As the result of air pollution control regulations on the branched chain ketonic solvents, the coatings industry has already started to use alternatives. This section reviews the following alternatives: reformulated solvent systems; high solids (organosols and plastisols); water based coatings; and powder coatings.

(1) Reformulation

Solvent reformulation consists of replacing the active component (ketone) in the solvent with an alternative. The reformulated blend must possess similar solution characteristics (resin solubility, viscosity, etc.) and evaporation characteristics to the original solvent. The branched chain ketones (e.g., MIBK and isophorone) have been replaced by straight chain ketones (e.g., MEK and cyclohexanone) (SRI, 1973; CMR, 1975a). Esters are the primary alternatives for formulating a ketone-free solvent (Klug, 1964; Wyart and Dante, 1969), but reformulation with esters results in a more costly solvent. Kline (1975) suggests that reformulating with conforming solvents will not be the trend; in part, this is due to the expense of the new solvent blend (Martens, 1968; Levy, 1973). Table 34 illustrates the cost differences between reformulation and the original solvent. Another disadvantage to reformulating is that new, more stringent air pollution regulations and new occupational standards could require another reformulation. Levy (1973) also noted that a reformulated solvent might release more pounds of reactive solvent even though it complies with standards.

Table 34. Comparison of Costs for Reformulating a Solvent Blend (From Levy, 1973)

Solvent		Reformulation	
Methyl ethyl ketone	14%	Methyl ethyl ketone	68%
Toluene	80%	Toluene	10%
2-Nitropropane	6%	Butyl acetate	22%
Cost	\$0.52/gal	Cost	\$0.94/gal
Reactivity	0.34[a]	Reactivity	0.13[a]

[a] Weighted reactivity by proportions of the compounds in the formula.

(2) High Solids and Powder Coatings

High solids formulations are dispersions of very fine resin particles mixed in the plasticizers, pigments and other compounds to yield a semi-liquid form. These can be either plastisols, which are formulated without solvent, or organosols, which contain some active solvents (including ketones) and hydrocarbon diluent (Dean, 1972c). High solids dispersions can be formulated with vinylic, polyester, or polyurethane resins and can be used to coat textiles or metal surfaces (Kline, 1975). Kline (1975) notes that the high solids systems have energy advantages over the conventional solvent systems and latex coatings.

Zimmt (1974) notes some disadvantages caused by occupational safeguards. Some high solids formulations use monomers (e.g., styrene and acrylate esters) as part of the liquid matrix, which are sometimes volatile and toxic. High solids coatings require radiation curing with either electron beam or ultraviolet irradiation. Since electron beams can create X-rays, heavy shielding is necessary or shielding is necessary to prevent eye damage when U.V. irradiation is used. In addition, the U.V. irradiation could generate some ozone and initiate photochemical smog production within the plant.

Powder coatings, which are formulated without solvent, are limited in application to metallic surfaces. Kline (1975) reports that only two techniques which have been developed have reached commercial acceptance: fluidized bed process and electrostatic spraying. In the fluidized bed process, the object to be coated is preheated above the melting point of the coating ingredients and then immersed in a suspension of the coating materials maintained by an upward air flow. Two disadvantages of this technique are that the minimum coating thickness is more than 5 mills and the film might be uneven. In electrostatic spraying, the powder is given an electric charge at the nozzle of the spray gun and the object to be coated is grounded. The coating is more evenly distributed and can be applied thinner (3-4 mills) than that applied by the fluidized bed process.

Powder coatings have reportedly met very limited success for automobile topcoatings. The technique is efficient for single color in a production line but poor if successive runs in a production line require different colors (Kline, 1975). Thus, its potential as an alternative is limited.

(3) Water-Based Coatings

The water-based coatings are reportedly the fastest growing segment of the industrial coatings market (Kline, 1975; Spence and Haynie, 1972). The resins formulated into water-based coatings include polyvinyl acetate and acrylics (Dean, 1972a,b,c). While the formulated solvent consists of at least 80% water, the remaining blend can include organic solvents. Glycols are the favored solvent (Ruhm, 1970), whereas ketones are poor solvents (May, 1973). The film properties from these formulations are reportedly equal to or superior to solvent-based coatings.

The water-based coatings can be applied by several methods: dip, flow or curtain coating; electrostatic, hot airless or steam spray; roll or coil coating; or electrodeposition (Kline, 1975). Spence and Haynie (1972), report that the spraying techniques are the most common currently used. However, it is electrodeposition that is expected to become the dominant method. Kline (1975) estimates that 200 electrodeposition tanks now exist in the U.S.

The usual technique has been to charge the metal object to be coated as the anode. The coating deposits uniformly to a maximum thickness of 1.0 to 1.5 mills (Spence and Haynie, 1972). Kline (1975) reports that PPG Industries is developing a cathode technique which is superior to the anodic procedure.

Electrodeposition requires a high capital investment. While the average cost is estimated between $100,000 and $250,000, costs go as high as $1.5 to $2.0 million for equipment for automotive body coating (Kline, 1975; Spence and Haynie, 1972). However, operating costs are reportedly lower, paint wastes are less, and curing time is shorter than for other application techniques (Kline, 1975).

The major uses of electrodeposition in order of decreasing importance are for the automotive industry, appliances, electrical equipment, metal furniture, and steel products. An impediment to its growth is the present inability of electrodeposition to topcoat automobiles. It is now used only for undercoatings, but technology is reportedly being developed to extend the techniques to topcoats as well. According to Spence and Haynie (1972), the industry must develop paints formulated with conductive solids for success in this application.

b. Other Solvent Uses

The function of solvents in adhesive formulations is similar to that in coatings. Just as in coatings, it is possible to reformulate a solvent blend (Blomquist, 1963).

The only solvent-free process listed for adhesives is the "hot-melt" or "fusible" system (Blomquist, 1963). The system uses adhesives which can be softened by heating and applied while heat softened. The disadvantage of this system is that the adhesive remains heat sensitive, so the applications are limited to systems which are not heated above the critical temperatures.

Other solvent systems can be used in place of those based on ketones for extraction purposes. For example, benzene-toluene or benzene-ethylene dichloride solvent systems can be used for lube oil dewaxing (Tuttle, 1968).

C. Environmental Contamination Potential

1. General

The sources of the selected ketones in the environment are not well defined. It is known that they are formed naturally, are emitted from industrial uses, and occur as a product of man's activity; but the relative importance of the sources of each ketone cannot be established with the evidence at hand. There is not sufficient information to estimate the total human exposure to these ketones.

Most of the selected ketones are naturally occurring. The straight chain ketones are frequently found in foods, where they are important components in natural flavoring. Man's food processing can increase their concentration. They are also produced in biological degradation of organic wastes by soil and water organisms. Man affects their production from organic wastes by the amounts of wastes disposed and the disposal techniques. The ketones are produced in air by the photooxidation of branched chain olefins. The hydrocarbons emitted from motor vehicles and from stationary sources include these branched chain olefin precursors.

Most information available on the direct release of ketones to the environment is related to ketonic vapors. The major sources of these emissions are the evaporation of ketonic solvents from surface coatings and allied industrial uses, vehicle emissions, losses from their production, and other sources (Spiller, 1973; Hoffman, 1970; Danielson, 1967). The relative contributions from each source is expected to vary for every ketone. For MEK, the evaporation of coating solvents is apparently the dominant source.

On the order of 300 million pounds of MEK are evaporated from industrial surface coating solutions annually, and a large percentage is apparently vented to the atmosphere without treatment to control its release. For other ketones, vehicle emissions could be a sizable contributor, if not, in fact, the major source. For example, the mesityl oxide released to the atmosphere with automobile exhaust is expected to be quite significant compared to the release of evaporated solvents from industrial coatings. While mesityl oxide is produced in about the same concentration as MEK in automobile exhaust, it is consumed in formulating coating solvents about one order of magnitude less than MEK. Also, it is expected that evaporated mesityl oxide will be reduced by a greater percentage than evaporated MEK prior to release of the solvent vapors to the atmosphere (see page 285). The major source of acetophenone emissions, according to Imasheva (1966), is from the cumene hydroperoxide process which produces phenol, acetone, and acetophenone as the major products.

2. From Production

There is not much published data on environmental contamination from ketone production. The only data available in the literature was limited to discussions of total organic carbon in waste water discharges (Sittig, 1974).

The processes by which the ketones are manufactured usually have closed reactor systems. The linear ketones are usually prepared by dehydrogenation of the corresponding alcohols; some MEK and cyclohexanone are produced by partial oxidation of the corresponding alkanes; some cyclohexanone is manufactured by phenol reduction; and most of the branched chain ketones are products of acetone (see Production, page 56). The potential for contamination arises from the incomplete condensation of ketonic vapors or their incomplete scrubbing from reaction gases prior to venting to the atmosphere; from fugitive emissions; from material transfers; and from accidental spillage. Water pollution potential arises if water is used as the scrubbing solvent. This potential is minimized when wash water is recycled or nonaqueous scrubbing solvents are used. Sludge and solid waste disposal by methods other than incineration is also a potential source of release to the environment (see Disposal, page 106).

3. From Transport and Storage

Ketone emissions to the atmosphere during transport and storage can result from accidental spillage, vapor losses during transfer operations, and venting losses from tanks. The annual amounts lost are unknown.

Dowd (1974) surveyed potential losses of solvent from storage and filling operations in paint and resin manufacture. He reported that 41% of all solvent storage tanks over 5,000 gallon capacity did not control venting losses. Controlled tanks, in general, were equipped with conservation vents.

Dowd (1974) calculated the solvent losses during filling operations (see Table 35). These losses are proportional on a weight basis to the product of the vapor pressure and molecular weight. According to Dowd, the filling losses are not controllable. Based on his estimates, typical ketone filling losses were calculated to range around 0.3 to 0.4 pounds/100 gallons of ketone. On a weight basis, the loss will be on the order of 50 pounds per million pounds. Evaporation losses will occur during each tank filling.

Table 35. Filling Losses For Selected Solvents at 20°C
(From Dowd, 1974)

Solvent	Vapor Pressure, at 20°C (mm)	Molecular Weight (g)	Filling Loss (lb/100 gal)
Acetone	186	58	0.494
Ethyl acetate	74	88	0.299
Toluene	22	92	0.0927
Mineral Spirits	2(est)	160(est)	0.0147

4. From Use

Evaporation of solvents from industrial surface coatings and related uses (e.g., printing inks and adhesives) release more of the selected ketones to the environment than all other uses. Virtually all solvents from coatings are evaporated. To prevent the ketonic vapors from reaching the environment, it is necessary to first collect the organic vapors and subsequently remove and ultimately dispose of the ketones (see Current Controls, page 110). In comparison, the ketone loss in processing solvents (e.g., lube oil dewaxing) is reported at ca. 1% (Tuttle, 1968) for each extraction.

The solvent losses during the formulation of the coating solutions are considered to be small (DiGiacomo, 1973; Dowd, 1974). Losses are attributed to fugitive emissions. Solvents evaporating during the resin cooking and thinning are collected by hoods and either incinerated or removed with activated carbon.

Specific information on the quantities of ketones lost to the atmosphere in actual operations is not available, but there does exist some information on the total emissions (Hoffman, 1970; Danielson, 1967; Bersowitz *et al.*, 1973) and the potential emissions (Hughes *et al.*, 1975). Hughes *et al.* (1975) have estimated the quantity of solvent evaporated from industrial coatings other than automobile and architectural painting. The predicted solvent evaporation values, which are summarized in Table 36 are estimates for weight of ketone lost per unit produced. They do not take into account any emissions control technology.

Table 36. Predicted Ketonic Solvent Evaporated from Some Industrial Coatings (From Hughes et al., 1975)

Product catagory	Product	Emissions factor for ketones (g. ketone/unit produced)
Paper and paperboard		---
Fabric treatment		---
Sheet, strip and coil	Metal Cans	2.657
	Duct work	8650.0
	Fencing	4119
	Wood paneling	3.83
	Canopies and awnings	4325
	Screening	3.83
	Metal doors (excluding garage doors)	175.1
	Gutters	8650
Major appliances	Refrigerators	120
	Driers	45.2
	Washers	33.7
	Enameled plumbing fixtures	---
Wood furniture	Bedroom furniture	3.7
Metal furniture	Filing cabinets	8650

Some perspective of the potential amount of ketone released to the atmosphere can be developed by inspecting the industrial surface coating operations and the required controls over organic content of ambient air and emissions. With solvent based coating solutions, the operations proceed through a production line which can be separated into three phases:

application of the coating solution; a flash-off period during which the solvent can evaporate at ambient temperature; and baking (National Paint and Coatings Association, 1975; Feldstein, 1974). The weights of solvent evaporated in each phase are not known. However, it is known that some residual solvent (7 to 10%) can remain after the baking (Gadomski et al., 1974).

Throughout the production line, atmospheric ketones must be maintained at a low enough concentration to conform to insurance standards and occupational health requirements (Baskin et al., 1971). This can be achieved by flushing with air and/or removing solvent vapors through ventilation hoods (see Current Controls, page 110).

The amount by which the ketone concentration is reduced before release to the atmosphere will be controlled to some extent by the air pollution regulations of each state. For most states, the regulations are similar to Los Angeles County's Rule 66 (see Regulations, page 285). In general, release of non-complying solvents (photoreactive solvents such as blends containing MIBK or diacetone alcohol) will require control. However, complying solvents need not be reduced except for those emitted from paint bake ovens (Feldstein, 1974; National Paint and Coatings Association, 1975). Under Rule 66, the reduction in solvent emissions is specified as 85%. Since most of the coatings industry uses incineration to control emissions (National Paint and Coatings Association, 1975), the ketone is destroyed rather than collected for disposal elsewhere (see Current Controls, page 110).

It is assumed that, in general, the surface coatings industry will release solvent vapors to the atmosphere with minimal control required by law. Thus, emissions of solvents blended with MEK, other linear, non-photochemically reactive ketones, and some of the branched chain ketones might only be controlled when they originate from the paint bake ovens. Branched chain ketones (e.g., MIBK), which are formulated into non-complying solvents and require reduction of all emissions, are less likely to be released to the atmosphere than the ketones in complying solvents.

5. From Disposal

Most of the waste ketones are generated from coating operations. According to industry sources (National Paint and Coatings Association, 1975), the ketones annually consumed by coating and allied industrial uses (e.g., adhesives) are neither recycled nor collected for disposal, but are directly incinerated or released to the atmosphere. The controls over these emissions are discussed in the section on environmental contamination potential from use, p. 95.

The information on other ketone wastes was insufficient for estimating the amounts disposed or the methods of disposal. There is some monitoring data on ketones in waste-water streams and landfill leachate (see Table 44, page 126).

Potential environmental contamination from disposal methods is included in the discussion on the recommended methods of disposal (see page 106). While potential losses from incineration are considered negligible (Besselievre, 1969), the potential exists for air and water contamination from disposal in sewage or into landfills (Abrams et al., 1975).

6. Potential Inadvertent Production in Other Industrial Processes as a By-Product

Inadvertent ketone production results from incomplete hydrocarbon oxidation, fermentation processes, and their release from natural substances during processing. This section will discuss ketone production from fuel burning, particularly in auto emissions, but excludes ketone production in food by biochemical processes such as fermentation. The latter will be discussed in the following section.

Small quantities of ketones are produced by the partial oxidation of petroleum fuels. Some quantitative data has been reported on the ketones in automotive emissions, but no information was found on ketone emissions from stationary sources. Ketone concentration in automotive emissions varies with the engine running conditions and fuel; their concentrations range from less than detectable quantities up to 1-2 ppm (Rose, 1962; Bellar and Sigsby, 1970; Seizinger and Dimitriades, 1972). The ketones (excluding acetone) and maximum concentrations reported are: MEK, 1.0 ppm; mesityl oxide, 1.5 ppm; 3-methyl-3-buten-2-one (methyl isobutenyl ketone), 0.8 ppm; methyl propyl (or isopropyl) ketone, 0.8 ppm; and acetophenone, 0.4 ppm (Seizenger and Dimitriades, 1972). Annual automotive hydrocarbon emissions have been estimated at 27.3 million tons (Council on Environmental Quality, 1974) with typical hydrocarbon concentrations of 900 ppm (American Chemical Society, 1969). While the ketones are relatively minor components in automotive exhaust emissions, the quantity emitted might be a significant contribution to their ambient atmospheric concentration. For example, if it is assumed that any one ketone occurs at an average concentration of 0.1 ppm, and total hydrocarbon concentration is approximately 1000 ppm, then annual ketone emission would be on the order of 5 million pounds. This production would be only a moderate contribution to the potential contamination from use of MEK, but could be a substantial contribution for the other ketones, such as mesityl oxide or methyl propyl ketone.

The syntheses of acetaldehyde and acetic acid appear to be the only major chemical processes which would yield significant amounts of ketonic products among those listed in Austin's (1974) survey of the 100 leading organic chemicals. In the controlled oxidation of commercial _n_-butane (95% _n_-butane, 2.5% isobutane and 2.5% pentane), conditions can be modified so that the major product is acetaldehyde, acetic acid, or MEK (Austin, 1974; Faith _et al_., 1965) (see Production, page 56). While the acetaldehyde production uses a vapor phase oxidation (_ca_. 100 psi and 700°C), acetic acid is produced by liquid phase oxidation (_ca_. 350°C and 800 psi) with cobalt or manganese acetates as the usual catalyst for both (Austin, 1974; Faith _et al_., 1965). In acetaldehyde production, Austin (1974) reported the product mixture includes acetone (4%) and mixed solvent (12%). In acetic acid production, Faith _et al_. (1965) included ketones in miscellaneous organic by-products (8% of the product mixture). Other processes are also used for acetaldehyde and acetic acid production which do not produce side-streams of ketone.

The ketones have been observed in effluents of coal gasification plants (Kavan and Basyrova, 1967, 1968) and kraft paper mills (Bethge and Ehrenborg, 1967). Small quantities of MEK, methyl isopropyl ketone, methyl _n_-propyl ketone, and diethyl ketone have been detected.

7. Potential Inadvertent Production in the Environment

The ketones are minor constituents of a wide number of foods. In some cases, man influences their concentration by fermentation processes, heat treatment, and other commercial processing (Chang, 1966).

Since ketones are important components of the food flavors, some of the compcunds (e.g., acetophenone, methyl nonyl ketone, methyl heptyl ketone) are important additives (Chang, 1966; Hamann and Guenther, 1966). Table 37 summarizes some of the lower molecular weight ketones observed in food stuffs. The information available in the literature is not sufficient for estimating the amount of ketones ingested in the diet.

Diacetone alcohol and mesityl oxide have been observed in foodstuffs exposed to acetone. They formed in meat carcasses which had been exposed to freshly painted surfaces where acetone was a component of the paint solvent. They were also found in vegetables and seeds, from which oil had been extracted with acetone (Fore _et al_., 1975; Patterson and Rhodes, 1967; Pearce _et al_., 1967).

Ketones are intermediate products in the biodegradation of organic compounds. Man influences biological ketone production by waste disposal methods. MEK and acetone have been identified as products of the activated sludge treatment of sewage (Malaney and Gerhold, 1962; Abrams _et al_., 1975) and as components of the leachate from solid waste (Borrows and Rowe, 1975; Abrams _et al_., 1975). Borrows and Rowe have measured fairly high concentrations of acetone in year old landfill leachate (_ca_. 0.60 g/ℓ). It is possible that the resulting acetone can subsequently yield condensation productions, such as diacetone alcohol. Diacetone alcohol has been identified as a minor component (2.9 mg/ℓ) in a landfill leachate, but no information was given concerning its source (Alford, 1975). The information at hand is not sufficient to allow a reasonable estimate of the potential inadvertent production of the ketones from waste disposal.

Table 37. Ketones Observed in Foodstuffs

Reproduced from best available copy.

Ketone	Commodity	Concentration	Reference
Methyl ethyl ketone	Cheeses		Nakanishi et al., 1965; Harper et al., 1962;
	(Swiss cheese)	0.3 ppm	Langler et al., 1967
	Milk	0.077-0.079 ppm	Wong and Patton, 1962
	Cream	0.154-0.177 ppm	Wong and Patton (1962)
	Milk fat	8 ppm	Lawrence and Hawke, 1963
	Roasted barley		Collins, 1971
	Bread		Wick et al., 1964
	Honey		Cremer and Riedmann, 1964
	Chicken		Minor et al., 1965
	Corn silage		Morgan and Pereira, 1962
	Oranges		Schultz et al., 1964; Dinsmore and Nagy, 1971
	Black tea		Yamanishi, 1965
	Rum		Fenarolli et al., 1965
	Tobacco		Chackraborty and Weybrew, 1963
Methyl n-propyl ketone	Cheeses		Nakanishi et al., 1965; Harper et al., 1962; Harvey and Walker, 1960;
	(Swiss cheese)	0.98 ppm	Langler et al., 1967
	Evaporated milk		Muck et al., 1963
	Milk	0.007-0.026 ppm	Wong and Patton, 1962
	Cream	0.025-0.045 ppm	Wong and Patton, 1962
	Bananas		Issenberg and Wick, 1963
	White bread		Wick et al., 1964
	Soybeans		Fujimaki et al., 1965
	Potato chips		Mookherjee et al., 1965
	Toasted oats		Hrdlicka and Janicek, 1964
	Tobacco		Chackraborty and Weybrew, 1963
Methyl n-butyl ketone	White bread		Wick et al., 1964
	Toasted oats		Hrdlicka and Janicek, 1964
	Milk	0.007-0.011 ppm	Wong and Patton, 1962
	Cream	0.017-0.018 ppm	Wong and Patton, 1962
Methyl isobutyl ketone	Oranges		Schultz et al., 1964
Methyl n-amyl ketone	Cheeses		Nakanishi et al., 1965; Harvey and Walker, 1960;
	(Swiss cheese)	0.45 ppm	Langler et al., 1967
	Evaporated milk		Muck et al., 1963
	Butter		Winter et al., 1963
	Milk		Wong and Patton, 1962
	Cream	0.004-0.007 ppm	Wong and Patton, 1962
	Milk fat	16 ppm	Lawrence and Hawke, 1963
	White bread		Wick et al., 1964
	Soybeans	1 ppm	Fujimaki et al., 1965
	Peaches		Broderick et al., 1966
	Orange juice		Dinsmore and Nagy, 1971

Ketones are minor constituents in photochemical smog (Altshuller, 1966; Altshuller and Bufalini, 1965, 1971; Haagen-Smit and Wayne, 1968). They are thought to be formed in photooxidative reactions of branched chain olefins with ozone. MEK, for example, is formed as a product in ozonation of 2-methyl-1-butene (Altshuller and Bufalini, 1971).

D. Current Handling Practices and Control Technology

1. Special Handling in Use

The Occupational Health and Safety Administration (OSHA) is in the process of establishing regulatory control over the industrial use of the ketones (see Current Regulations - OSHA, p. 286). Practices which have previously been recommendations will become legal requirements (Manufacturing Chemists Association, 1961, 1962). The OSHA standards on ketones seek occupational protection against inhalation and dermal contact and prevention of fire or explosion (OSHA, 1975d).

The OSHA standards do not consider respirators an adequate substitute for reducing ambient concentrations of ketones. If the engineering and work practice controls cannot reduce concentrations below the permissible levels (see Table 105, p. 287), the concentration must be reduced to the lowest feasible level, and workers must then wear an appropriate respiratory device.

Plant locations where the ketone vapors are present have been designated as Class I, Group D, under the National Electrical Code (NEC). This requires that all electrical wiring and electrical equipment (e.g., lighting, relays, motors, controls and switches) must be explosion-proof or otherwise conform to the NEC Article 500 (MCA, 1961, 1962).

In case of spills, all potential sources of ignition must be eliminated, the area must be ventilated, and the spill cleaned up immediately.

If a worker's clothing becomes wet with any of the ketones designated as flammable liquids (see p. 286), the worker must immediately remove them until they have dried.

2. Methods for Transport and Storage

Since the ketones are combustible, transport and storage techniques must provide protection against fire and explosion hazards. Methods are often regulated by federal, state, and local agencies. The U.S. Department of Transportation (DOT) lists some of the ketones as flammable liquids (e.g., MEK and MIBK) but not other ketones (e.g., diacetone alcohol) (United Parcel Service, 1973). State and local agencies enforce intrastate transportation and storage regulations. These are often adopted from model codes of the National Fire Protection Association (MCA, 1961, 1962; NFPA, 1974, 1975).

The ketones can be transported in tank cars, tank trucks, metal barrels or drums (55 gallon), metal cans and polyethylene bottles (up to 10 gallons maximum), and glass bottles (up to 1 gallon maximum) (NFPA, 1975; United Parcel Service, 1973; MCA, 1961, 1962). In interstate shipments, containers and vehicles must be placarded and conform to the requirements of the DOT. These are detailed in the MCA's Chemical Safety Data Sheets (MCA, 1961, 1962).

In loading and unloading containers or tankers, precautions must be taken against fire hazards. This includes grounding metal drums or tankers, using spark resistant tools, and designation of dock areas as Class I hazardous locations as defined by the National Electric Code (MCA, 1961, 1962; NFPA, 1975).

Storage tanks should be outside of any building. NFPA (1974) suggests that underground tanks should be located at least one foot from existing building foundations and supports, and at least three feet from the nearest line of adjoining property that might be built upon. Tanks should not receive any of the load from a building foundation. Above-ground tanks should be in remote areas at least 25 feet from any important building. Above-ground tanks should be diked in case of rupture, and vented or equipped with pressure relieving devices (MCA, 1961, 1962).

NFPA (1975) suggests that outside or detached storage is preferred to indoor storage. Indoor storage should be in a standard flammable liquid storage room or cabinet. The ketones should be segregated from oxidizing material. Containers should be protected against physical damage. The area should be kept cool and well vented, and should be equipped with automatic sprinklers or some adequate extinguishing system. Storage rooms should be pitched to trapped floor drains (MCA, 1961, 1962; NFPA, 1974, 1975).

3. Disposal Methods

The favored disposal method for the selected ketones is incineration (MCA, 1961, 1962; Besselievre, 1969). Combustion efficiency is better than 99.99% (Abrams et al., 1975).

Disposal through conventional sewage systems should not be used for disposal of large quantities of the ketones, but could be acceptable for small quantities. Discharge of large quantities into a sanitary sewer creates the hazard of an explosion (United Parcel Service, 1973; MCA, 1961, 1962). If the discharge is diluted with large quantities of water, the explosion danger is eliminated. Activated sludge will effectively degrade some of the selected ketones. The efficiency of activated sludge is given as: MEK, 90%, and acetophenone, 90% (Abrams et al., 1975). However, Gaudy et al. (1963) observed that under the conditions for activated sludge treatment in a sewage treatment plant, MEK is very resistant to sludge biodegradation and would evaporate to the atmosphere more rapidly than it would biodegrade.

If the selected ketones are land disposed, they can either evaporate to the atmosphere or migrate with leachate (Abrams et al., 1975; Garland and Mosher, 1975). While soil bacteria will degrade ketones in a period estimated at 1 to 2 months, Abrams et al. (1975) note that if high industrial waste loadings are present, the biodegradation rate could be slowed. They concluded that if land disposed, large quantities of the ketones are a contamination threat.

The MCA (1961, 1962) recommends that, prior to their disposal, metal containers which formerly contained acetone or MEK should be drained and then steamed.

4. Accident Procedures

The emergency response to accidental spillage of the selected ketones is principally concerned with the prevention or the suppression of fire (NFPA, 1975; United Parcel Service, 1973). The United Parcel Service (1973) suggests the following procedure for spills of the water soluble ketones:

Personnel:

Wear protective clothing and for high concentrations wear gas mask. Wash skin and eyes thoroughly if contacted. Remove and wash contaminated clothing.

Vehicle or Facility:

Hose down with water. Dry with commercial, non-organic drying agent.
Do not allow waste liquid to enter sewer system.

For the water insoluble ketones, the response is modified as follows:

Vehicle or Facility:

> Rinse area of spill with alcohol and then with plenty of water. Repeat until all of the chemical has been removed. Dry with commercial, non-organic drying agent. Do not allow waste liquid to enter sewer system.

Table 38 summarizes the hazard ratings and fire fighting information for selected ketones. Fire fighters working in the vicinity of the ketones should wear full protective gear, including a respiratory device (NFPA, 1975). The NFPA system rates health, flammability, and reactivity on a scale from 0 to 4, with zero being the safest category. All ketones received a reactivity rating of zero, which NFPA defines as, "materials which are normally stable even under fire exposure conditions and which are not reactive with water. Normal fire fighting procedures may be used." The ketones range in health ratings from 1 to 3. These ratings are defined as follows:

3 Materials extremely hazardous to health, but areas may be entered with extreme care. Full protective clothing, including self-contained breathing apparatus, rubber gloves, boots and bands around legs, arms and waist should be provided. No skin surface should be exposed.

2 Materials hazardous to health, but areas may be entered freely with self-contained breathing apparatus.

1 Materials only slightly hazardous to health. It may be desirable to wear self-contained breathing apparatus.

The ketones received flammability ratings of 2 or 3. These are defined as:

3 Liquids which can be ignited under almost all normal temperature conditions. Water may be ineffective on these liquids because of their low flash points. Solids which form coarse dusts, solids in shredded or fibrous form that create flash fires, solids that burn rapidly, usually because they contain their own oxygen, and any material that ignites spontaneously at normal temperatures in air.

2 Liquids which must be moderately heated before ignition will occur and solids that readily give off flammable vapors. Water spray may be used to extinguish the fire because the material can be cooled to below its flash point.

Table 38. Accidental Spill Response Information
(From NFPA, 1975)

	Hazard Identification			Fire
Ketone	Health[a]	Flammability[a]	Reactivity[a]	Fighting Phases[b]
Acetophenone	1	2	0	3
Acetone	1	3	0	1
Cyclohexanone	1	2	0	2
Ethyl butyl ketone	1	2	0	3
Methyl ethyl ketone	1	3	0	1
Isophorone	2	2	0	3
Methyl isobutyl ketone	2	3	0	3
Mesityl oxide	3	3	0	2

[a] For definition of the numerical rating, see the text.

[b] Fire Fighting Phases:

1. Use dry chemical, "alcohol" foam, or carbon dioxide; water may be ineffective, but water should be used to keep fire-exposed containers cool. If a leak or spill has not ignited, use water spray to disperse the vapors and to protect men attempting to stop a leak. Water spray may be used to flush spills away from exposures and to dilute spills to nonflammable mixtures.

2. Use water spray, dry chemical, "alcohol" foam, or carbon dioxide. Use water to keep fire-exposed containers cool. If a leak or spill has not ignited, use water spray to disperse the vapors and to protect men attempting to stop a leak. Water spray may be used to flush spills away from exposures and to dilute spills to nonflammable mixtures.

3. Use water spray, dry chemical, foam, or carbon dioxide. Use water to keep fire-exposed containers cool. If a leak or spill has not ignited, use water spray to disperse the vapors and to provide protection for men attempting to stop a leak. Water spray may be used to flush spills away from exposures.

5. Current Controls

Control of the ketonic solvents emitted from industrial coatings has been well developed. The control technology consists of two stages: collection of the effluent gases, and removal of ketones and other solvents.

The most often used methods for removing solvent vapors from the effluent air are incineration and carbon adsorption (Danielson, 1967; Baskin et al., 1971; Mattia, 1970). Scrubbing the organic vapors is not efficient and is usually used as a first stage, before adsorption or incineration (Cooper, 1969; Mattia, 1970). With carbon adsorption the collected solvent could be either recycled or degraded (Cooper, 1969; Mattia, 1970). The economics upon which the choice of air pollution technology is based depend in part upon the capital and operating costs, value of recovered solvent, and future plant expansion.

Ketones, as well as other organic solvents, can be oxidized by direct or catalytic incineration. In either process, the amount of organic emissions that are eliminated depends upon the incineration temperature (Danielson, 1967; Gadomski et al., 1974). Table 39 compares the removal efficiency for the catalytic and direct flame combustion of organic vapors emitted from metal decorating industry sources. The direct flame afterburners reduced organic gases somewhat more than the catalytic incinerator (Danielson, 1967; Gadomski et al., 1974). Baskin et al. (1971) noted that the catalytic incinerator has an economic advantage over direct flame units. A typical catalytic incineration system is illustrated in Figure 13.

Table 39. Efficiency of Organic Emissions Reduction by Thermal and Catalytic Incineration

(From Gadomski *et al.*, 1974)

Type of Incineration	Incineration Temperature (°F)	Inlet Concentration (ppm) Min. Max.	Outlet Concentration (ppm) Min. Max.	CO[a] Outlet (ppm) Min. Max.	Efficiency (%) Min. Max.
Thermal	900	2860-15574	58-898	882-1259	79.44-99.58
	1000	2860-15574	5-440	n.d.-1169	89.93-99.96
	1100	2894-3474	102-188	349-548	94.10-96.80
	1200	2860-15574	7-77	n.d.-85	98.70-99.95
	1300	2894-3474	25-35	trace-127	98.90-99.20
	1400	2860-15574	1-15	n.d.	99.89-99.98
	1480	2894-3474	20-46	702-877	98.56-99.38
	900-1480	2860-15574	1-898	n.d.-1259	79.44-99.98
			Average Efficiency, thermal incineration		97%
Catalytic	600	801-3436	179-924	97-124	52.79-90.86
	700	801-16534	30-175	42-285	91.06-99.70
	800	801-16534	43-205	140-295	89.53-99.56
	850	801-3436	171-230	250-258	88.53-99.56
	900	801-3436	112-147	237-351	92.45-94.28
	950	801-3436	32-174	n.d.-176	91.12-98.37
	1000	801-3436	149-156	156-216	92.03-92.39
	600-1000	801-16534	30-924	n.d.-351	52.79-99.70
			Average Efficiency, catalytic incineration		90%

---

[a] May include inlet CO.

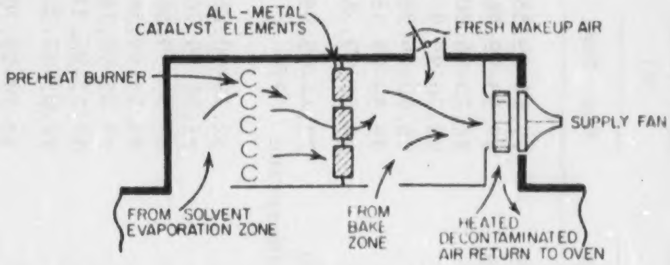

ALL-METAL CATALYST ELEMENTS
FRESH MAKEUP AIR
PREHEAT BURNER
SUPPLY FAN
FROM SOLVENT EVAPORATION ZONE
FROM BAKE ZONE
HEATED DECONTAMINATED AIR RETURN TO OVEN

Figure 13. Typical Catalytic Combustion System for Paint Bake Oven (Baskin _et al._, 1971)

(Reprinted with permission from UOP Air Correction Division)

In the adsorption technique for removing solvent vapors, the methods using activated carbon are predominant (Cooper, 1969). In the most commonly used systems, two adsorbing vessels are used (Cooper, 1969; Mattia, 1970). While one vessel is in use, the carbon in the other vessel is being regenerated. Carbon adsorption systems using moving-bed or fluidized bed designs have also been reported (Cooper, 1969). The carbon can be regenerated either with steam or with hot air. Figures 14 and 15 chart the flow of two modifications of the ZORBCIN process for regenerating spent carbon with hot air. In the former the collected organics are incinerated, while in the latter they are recycled.

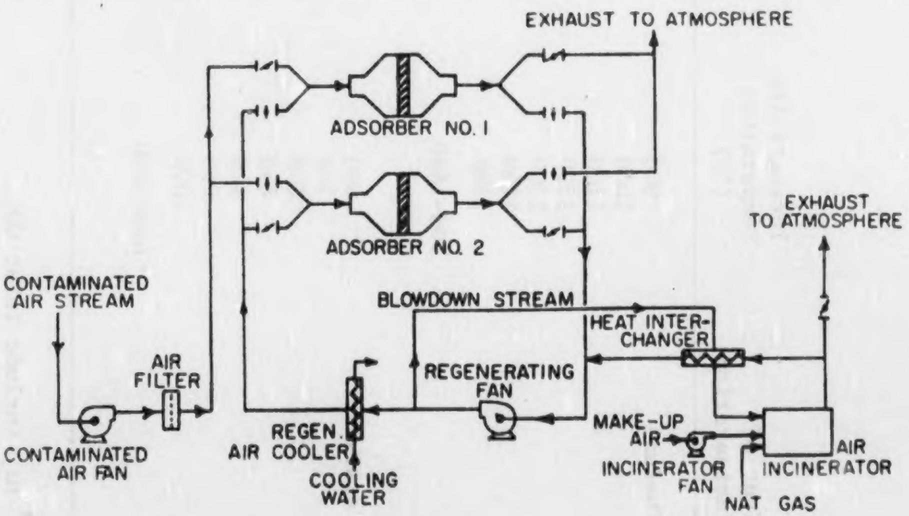

EXHAUST TO ATMOSPHERE
ADSORBER NO. 1
ADSORBER NO. 2
EXHAUST TO ATMOSPHERE
CONTAMINATED AIR STREAM
BLOWDOWN STREAM
HEAT INTER-CHANGER
AIR FILTER
REGENERATING FAN
REGEN. AIR COOLER
MAKE-UP AIR
CONTAMINATED AIR FAN
COOLING WATER
INCINERATOR FAN
AIR INCINERATOR
NAT GAS

Figure 14. ZORBCIN Process For Purifying Contaminated Air Streams (From Mattia, 1970) (Reprinted with permission from the American Institute of Chemical Engineers)

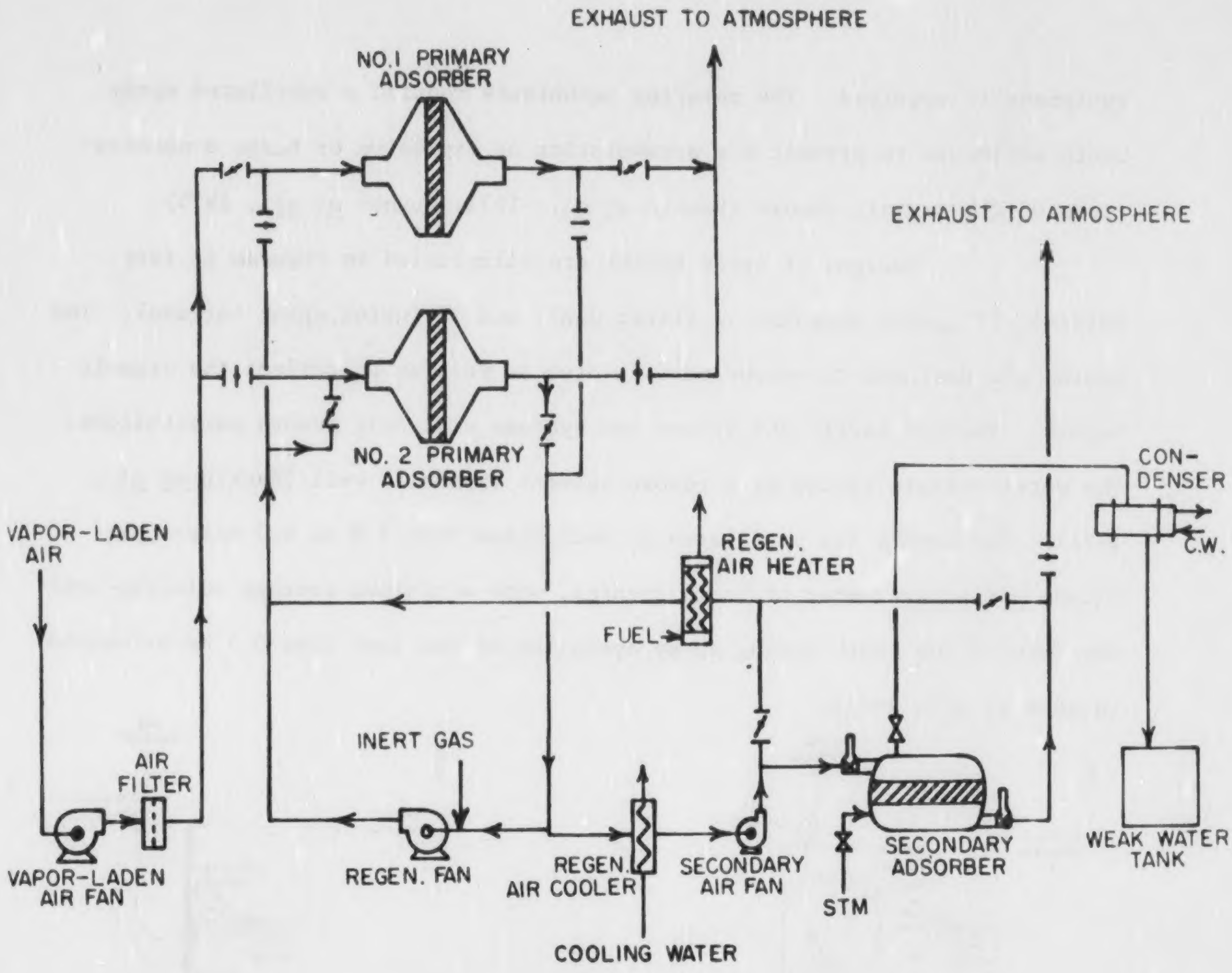

EXHAUST TO ATMOSPHERE
NO.1 PRIMARY ADSORBER
EXHAUST TO ATMOSPHERE
NO. 2 PRIMARY ADSORBER
CON-DENSER
C.W.
VAPOR-LADEN AIR
REGEN. AIR HEATER
FUEL
INERT GAS
AIR FILTER
SECONDARY ADSORBER
WEAK WATER TANK
VAPOR-LADEN AIR FAN
REGEN. FAN
REGEN. AIR COOLER
SECONDARY AIR FAN
STM
COOLING WATER

Figure 15. Cascade Adsorber Process For Recovering Solvents From Dilute Vapor-Laden Air Streams (From Mattia, 1970) (Reprinted with permission from the American Institute of Chemical Engineers)

The four most popular methods for the application of industrial coatings are dipping, flow coating, coil or roller coating, and spray (Baskin et al., 1971; Hughes et al., 1975). Canopy hoods are suitable for removing any organic vapors emitted from the first three methods. With spraying techniques, overspray can run from 30 to 90% (Baskin et al., 1971), so more sophisticated equipment is required. The spraying techniques require a ventilated spray booth enclosure to prevent the accumulation of explosive or toxic concentrations of the organic vapors (Baskin *et al.*, 1971; Hughes *et al.*, 1975).

Designs of spray booths are illustrated in Figures 16 (dry baffle); 17 (paint arrester or filter pad); and 18 (water spray curtain). The booths are designed to remove particulates as well as to collect the organic vapors. The dry baffle and filter pad systems will only remove particulates; the water-curtain system will remove solvent vapors as well (Baskin *et al.*, 1971). The booths are ventilated at velocities from 2.8 to 4.3 meters per minute per square meter of booth opening, with a minimum average velocity over the face of the booth during spray operation of not less than 0.5 meter/second (Hughes *et al.*, 1975).

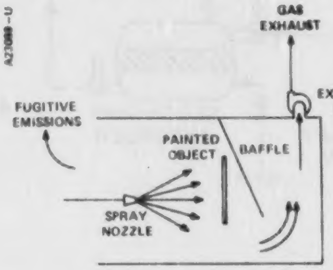

GAS
EXHAUST
EXHAUST
FAN
FUGITIVE
EMISSIONS
PAINTED
OBJECT
BAFFLE
SPRAY
NOZZLE

Figure 16. Dry Baffle Spray Booth (Hughes *et al.*, 1975)

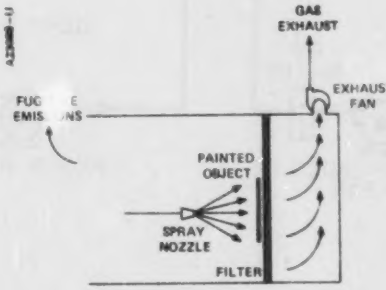

GAS
EXHAUST
EXHAUST
FAN
FUGITIVE
EMISSIONS
PAINTED
OBJECT
SPRAY
NOZZLE
FILTER

Figure 17. Filter Pad or Paint Arrestor Spray Booth (Hughes *et al.*, 1975)

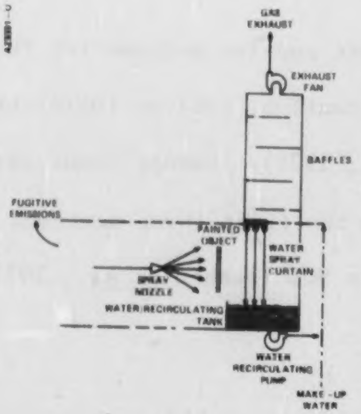

GAS
EXHAUST
EXHAUST
FAN
BAFFLES
FUGITIVE
EMISSIONS
PAINTED
OBJECT
WATER
SPRAY
CURTAIN
SPRAY
NOZZLE
WATER RECIRCULATING
TANK
WATER
RECIRCULATING
PUMP
MAKE-UP
WATER

Figure 18. Water-Wash Spray Booth (Hughes *et al.*, 1975)

Paint bake ovens are built to standards set for fire and explosion prevention. The vapor levels must not exceed the lower explosive limits (LEL) of the organic vapor (Danielson, 1967; Baskin et al., 1971). The amount of air needed for dilution is computed with a factor of safety from 4 to 12. Other requirements of the oven are that the vapor concentration must be less than the level of toxicity during loading or unloading (Baskin et al., 1971).

Paint ovens can be designed for batch operation (Figure 19) or continuous operation (Figure 20). They are designed with bottom ventillation, since the organic solvents are generally heavier than air (Danielson, 1967).

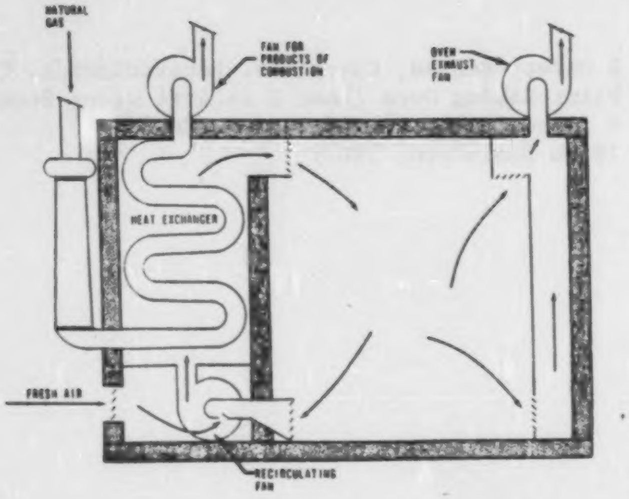

NATURAL GAS
FAN FOR PRODUCTS OF COMBUSTION
OVEN EXHAUST FAN
HEAT EXCHANGER
FRESH AIR
RECIRCULATING FAN

Figure 19. An Indirectly Heated, Gas-Fired, Recirculating, Batch-Type Paint-Baking Oven (From Danielson, 1967)

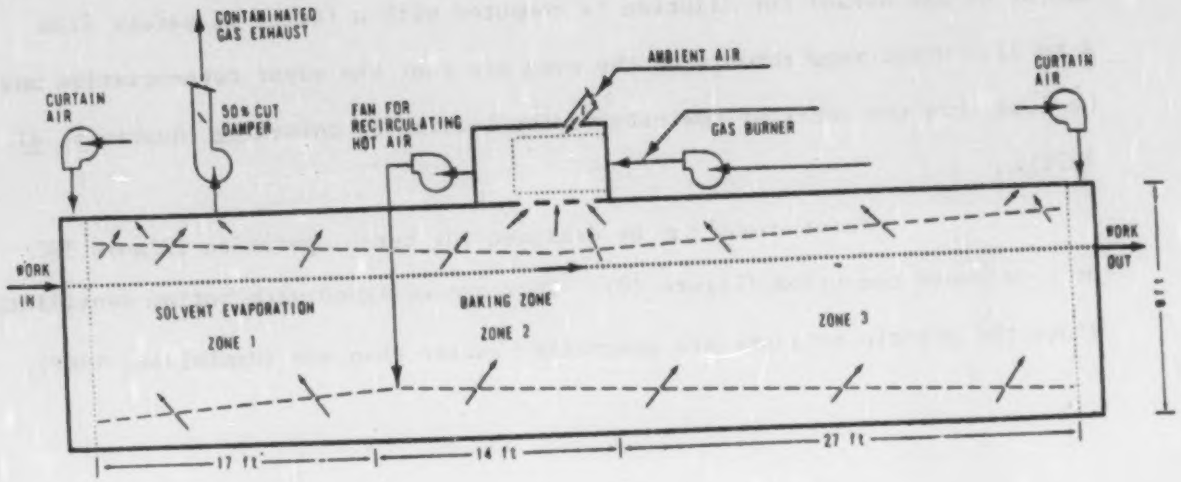

CONTAMINATED GAS EXHAUST
AMBIENT AIR
CURTAIN AIR
50% CUT DAMPER
FAN FOR RECIRCULATING HOT AIR
GAS BURNER
CURTAIN AIR
WORK IN
WORK OUT
SOLVENT EVAPORATION
ZONE 1
BAKING ZONE
ZONE 2
ZONE 3
8 ft
17 ft
14 ft
27 ft

Figure 20. A Direct-Heated, Gas-Fired, Recirculating, Continuous Paint-Baking Oven (Zone 1 is 4 ft wide; Zone 2, 5 ft 4 inches wide; Zone 3, 4 ft wide) (From Danielson, 1967)

E. Monitoring and Analysis

1. Analytical Methods

Gas chromatography (g.c.) is currently the most well developed technique for analyzing trace quantities of ketones (Analytical Quality Control, 1972; Webb et al., 1973). Flame ionization detection (FID) is the most sensitive detection technique now available for the selected ketones (Webb et al., 1973; Fishbein, 1972). Coatings based on silicone polymers and glycols, especially carbowax and DEGS, are the most frequently used packing materials in the columns (Analabs, 1974; Fishbein, 1972). While peak assignment in the past was based upon relative retention time, gas chromatographic-mass spectral (g.c.-m.s.) instrumentation is now commonly used to confirm the assignments (Webb et al., 1973).

The organization of g.c. data has been simplified by the Kovats Retention Index System for tabulating relative retention times (Caroff et al., 1966; Anderson, 1968). The relative retention time RT_f is the ratio of RT_s (retention time of the sample) ÷ RT_r (retention time of a reference hydrocarbon). The system is quite useful for standardizing analytical procedures between laboratories which are performing quality control, monitoring or surveillance (Anderson, 1968). Anderson (1968) has noted the following sources of error in determining the Kovats Retention Indices: instrumentation (from changes in carrier gas flow and column temperature); stationary phase degradation, especially by oxidation; adsorption on the stationary phase, especially when the polarity between the stationary phase and the sample is high; non-linear response caused by changes in gas flow and column temperature; and overlapping peaks. Indices based on hexane are tabulated for selected ketones in Table 40.

Table 40. Kovats Retention Indices For Selected Ketones
(From Anderson, 1968)

	DC-401 Column	DEGS Column	Apiezon L Column	Thermal Conductivity Detector (T.C.) Response Factor	Flame Ionization Detector (F.I.D.) Response Factor
Acetone	466 ± 29	1053 ± 29	472 ± 20	0.87	2.10
Methyl ethyl ketone	560 ± 9	1127 ± 14	553 ± 15	0.70	0.98
Methyl propyl ketone	640 ± 29	1203 ± 14	648 ± 16	1.49	1.33
Methyl isoamyl ketone	698 ± 10	1343 ± 14	704 ± 37	1.47	1.27
Methyl isobutyl ketone	714 ± 17	1217 ± 14	692 ± 14	0.72	0.78
Mesityl oxide	792 ± 15	1382 ± 14	776 ± 29	1.87	1.86
Cyclohexanone	894 ± 11	1757 ± 14	898 ± 16	.70	0.97
Diisobutyl ketone	961 ± 15	1430 ± 25	945 ± 8	1.20	1.07
Methyl heptyl ketone	1076 ± 12	1590 ± 25	1059 ± 7	0.65	0.60
Isophorone	1121 ± 3	2110 ± 28	1124 ± 7	0.77	0.86
Methyl nonyl ketone	1276 ± 7	1813 ± 29	1263 ± 6	1.18	1.14

Chromatographic Conditions

(1) Columns: 1) 10' x 1/8" s.s.-10% DC-401 on 60-80 mesh Gas-Pak WAB
2) 6' x 1/4" copper-30% DEGS on 60-80 mesh Gas-Pak WAB
3) 10' x 1/8" s.s.-10% Apiezon L on 60-80 mesh Gas-Pak WAB

(2) Column temperature 150°C

(3) Carrier gas: Helium with a flow rate of 50 ml/min measured with a soap bubble flow meter.

(4) T.C. Detector: Operating temperature 225°C
Filament current 150 ma.

(5) F.I.D. Detector: H_2 flow rate 20 ml/min.
Air flow rate 40 ml/min.
Operating temperature 250°C

(6) Sample size: 0.1-0.5 μl

(7) Recorder chart speed: 0.5, 1.0, 2.0 inches per minute

Table 41 lists some g.c. analyses reported for the selected ketones. The sample pretreatment is the critical factor in the analyses. At the minimum, the pretreatment must remove interferences and quantitatively transfer the ketones either to air or to a suitable organic solvent (e.g., freon or chloroform). For example, auto emissions have large quantities of hydrocarbons whose retention times are of the same order as the ketones. The carbonyls have been successfully isolated from the hydrocarbons by the use of cutter columns (Bellar and Sigsby, 1970) and by preparation of carbonyl derivatives (such as the dinitrophenylhydrazones and bisulfites) (Ellis et al., 1965; Barber and Lodge, 1963). The sensitivity of the analysis depends on the ability of the technique to concentrate the ketones from large samples (Analytical Quality Control, 1972; Webb et al., 1973; Bellar and Lichtenberg, 1974).

Air samples containing ketones can be collected and pretreated in the field or collected in Tedlar bags and pretreated in the laboratory. Schuetzle et al. (1975) noted that polyethylene, Saran, and Mylar are not suitable because of leakage. However, only a slight loss of MIBK occurred after 45 hour storage in a Tedlar bag (see Figure 21). Air samples can be concentrated and pretreated by cold trapping (Ellis et al., 1965), by adsorption (Mueller and Miller, 1974; Jenkins, 1973, 1974; Bellar and Sigsby, 1970), by collection in solvents (Ellison and Wallbank, 1974), and by preparing derivatives (Ralls, 1960; Barber and Lodge, 1963; Soukup et al., 1964; Jones and Monroe, 1965; Dinsmore and Nagy, 1971). While the preparation of derivatives (especially the dinitrophenylhydrazones) is an excellent method for isolating carbonyls, the technique does not quantitatively collect the ketones. Selective adsorption can isolate carbonyls with excellent results, but requires rather sophisticated instrumentation (Bellar and Sigsby, 1970).

Table 41. Analysis of the Selected Ketones by Gas Chromatography

Reference	Type of Sample	Isolation and Concentration	Detection	Compounds Studied	Sensitivity or Limits of Detection	Remarks
Corwin (1969)	Sea water	Sampled the headspace gases	GC (FID)	Acetone and methyl ethyl ketone	<5 μg/ℓ	
Smoyer et al. (1971)	Air	Sampled in stainless steel tubes	GC-MS (FID)	Acetone and methyl ethyl ketone	ppm	
Bellar and Sigsby (1970) Seizinger and Dimitriades (1972)	Automotive emissions	Isolated ketones from hydrocarbons by a cutter column; backflush to analytical column	GC (FID)	Acetone, methyl ethyl ketone, and mesityl oxide	0.05 ppm	Cutter column [1,2,3-tris(cyanoethoxy)propane] holds oxygenates
Ellis et al. (1965)	Automotive emissions	Isolated ketones from hydrocarbons by scrubbing through a 1% $NaHSO_3$ train. Thermal regeneration of ketones.	GC (TC)	Acetone and methyl ethyl ketone	5 ppm	Scrubbing does not quantitatively remove higher molecular weight ketones
Jenkins et al. (1973, 1974)	Air	Concentration by adsorption on Chromosorb 102, backflush to analytical column	GC-MS (FID)	Cyclohexanone	Emission $<1 \times 10^{-15}$ g/cm^2 sec	Measured rate of emission rather than concentration
White et al. (1970) Cooper et al. (1971)	Air (occupational surveillance)	Concentration by adsorption on activated carbon, desorption by CS_2	GC (FID)	Methyl ethyl ketone	<20 ppm	Better than 90% recovery
Mueller and Miller (1974)	Air (occupational surveillance)	Concentration by adsorption on activated carbon, desorption by CS_2	GC (FID)	Methyl ethyl ketone and diacetone alcohol	<25 ppm	About 60% recovery for diacetone alcohol
Grob and Grob (1971)	Air	Concentration on cigarette filter charcoal	GC (FID)	Acetophenone		
Burnham et al. (1972)	Drinking water	Concentration on XAD-2 or XAD-T resin	GC-MS (FID)	Methyl isobutyl ketone	Better than 1 ppb for neutral organics	
Kuwata et al. (1974)	Air	Concentration on Tenax G	GC (FID)		ppb level	
Austern et al. (1975)	Waste water	Freon extraction and concentration	GC-MS (FID)	Acetophenone	1.1 ng	87.9 ± 2.2% recovery of samples spiked 0.013-11.0 mg/ℓ
Keith (1974)	Waste water	Chloroform extraction and concentration	GC-MS (FID)	Diacetone alcohol and acetophenone	ppb level	
Ellison et al. (1974)	Waste water and waste sludges	Steam distillation and partition into cyclohexanone	GC-IR (FID)	Methyl isobutyl ketone	1 ml	Poor recovery (38% at 0.5 mg/ℓ; 51% at 20 mg/ℓ)
Dinsmore and Nagy (1971)	Liquid (orange juice)	Stripping with N_2 stream, collection as 2,4-dinitrophenylhydrazone derivative. Regeneration of carbonyl by flash thermal method	GC-MS (FID)	Acetone, methyl ethyl ketone, C-5 ketones		
Zlatkis and Liebich (1971) Zlatkis et al. (1973)	Liquid (urine)	Strip with N_2 stream, collected on Tenax G.C.	GC-MS (FID)	MEK, methyl n-propyl ketone and methyl n-amyl ketone		
Fore et al. (1975)	Solid (oil seeds)	Direct elution (with water) onto analytical column	GC (FID)	Mesityl oxide and diacetone alcohol	2 ppm	

GC- Gas chromatography
MS- Mass spectrometry
TC- Thermal conductivity detection
FID- Flame ionization detection
IR- Infrared spectrometry

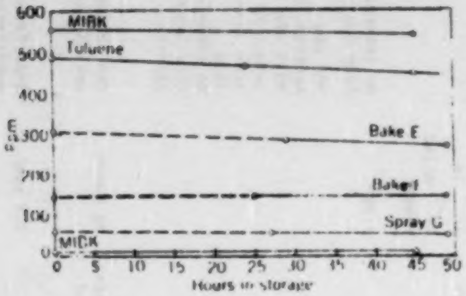


Figure 21. The Effect of Storage Time on Sample Recovery from Tedlar Bags (From Schuetzle et al., 1975) (Reprinted with permission from the Air Pollution Control Association)

Since water is not a suitable solvent for g.c. analysis, aqueous ketones must be transferred to another phase. Techniques used with aqueous samples include headspace sampling (Corwin, 1969), liquid-liquid extraction (Austern et al., 1975; Keith, 1974), distillation or stripping with an inert carrier gas stream (Ellison and Wallbank, 1974; Dinsmore and Nagy, 1971; Webb et al., 1973), and adsorption (Burnham et al., 1972). Headspace sampling is quite convenient in the absence of interferences. Extraction techniques for the lower molecular weight ketones are limited by their water solubilities (Webb et al., 1973; Ellison and Wallbank, 1974). Their solubility also limits the quantitative transfer by gas stripping techniques. Bellar and Lichtenberg (1974) found that only 20% of MEK (10 ml sample at 100 ug/ℓ) was removed by a 300 mℓ purge with N_2 (20 mℓ/min) compared to quantitative stripping of identically sized samples of methylene chloride, chloroform, and benzene. The concentration of low molecular weight ketones on synthetic resins has given excellent detection limits and recovery (Burnham et al., 1972).

Table 42 lists analytical methods other than gas chromatography. Most of the listed techniques are primarily useful for occupational

Table 42. Analytical Techniques for Selected Ketones Other Than Gas Chromatography

Reference	Type of Sample	Pretreatment	Analytical Method	Ketones	Sensitivity on Limits of Detection	Remarks
Munson and Hodgkins (1975)	Liquid		Spot test: Reagents are 2,3-dimethyl-2,3-bis-(hydroxylamino)-butane and either sodium metaperiodate or lead dioxide.	Aliphatic ketones	100-2000 μg	Sensitivity decreases with increasing substitution.
Kramer et al. (1971, 1972)	Aqueous		Fluorometric assay with o-nitrobenzaldehyde at pH 12.5.	α-methyl ketones	10^{-4} to 10^{-2} molar range	
Kacy and Cope (1955)	Air	Concentrated by collection in glacial acetic acid.	Color development (at 870 nm) with phosphomolybdic acid.	Isophorone	1 ppm	No interference from CO_2 up to 300 ppm Acetone, MEK and MIBK are three orders of magnitude less sensitive
Andrew et al. (1971)	Air	Collect vapors in water.	Color development with H-acid (4 amino,-5 hydroxy-naphthalene-2,7-disulfonic acid).	Cyclohexanone and methyl cyclohexanone		No interference from acylic ketones.
Afghan et al. (1975)	Aqueous	Amine derivative formation.	Twin sweep voltametry	Aliphatic ketones Acetophenone and benzophenone	ng range	The method is not well developed.
Wilks (1973)	Air	None	Infrared	See Table d.	0.1 ppm	Interference by substrates absorbing at the specified wavelength.
MacPhee and Kuramoto (1969)	Air	Collection in cold trap	Reaction with Rhodamine B dye and FIA; elution on silica gel.			Screening technique for oxygenated hydrocarbons.
Eberle et al. (1974)	Water	Does not require pretreatment.	Differential pulse polarography	Nonvolatile ketones only.		

health surveillance or as screening tests. Since the infrared technique can measure airborne ketone without a sample collection, it is quite useful for field analysis and monitoring in the absence of interferences (Wilks, 1973). The MIRAN portable infrared gas analyzer is equipped to measure ambient air at a single wavelength. The system has a variable cell pathlength, a scale expandable from 1 x 20 x, and a variable wavelength setting. Table 43 summarizes the settings to be used for analyses of the selected ketones and the minimum detection for each (Wilks, 1973).

Table 43. Data For Ambient Air Analyses of Ketones Using the MIRAN Gas Analyzer

	Maximum Allowable Exposure (8 Hour Weighted Average)			Minimum Concentration which the MIRAN Analyzer can detect	Absorbance Equivalent to the OSHA Limit		
Compound	PPM	mg/M^3	Analytical Wavelength μ	PPM	Absorbance	Scale Expansion	Pathlength M
Acetone	1000	2400	8.2	0.09	0.49	1	2.25
MEK	200	590	8.5	0.08	0.68	1	20.25
Cyclohexanone	50	200	8.3	0.3	0.1	1	20.25
Diacetone alcohol	50	240	8.5	0.8	0.25	1	20.25
Diisobutyl latone	50	290		NA	NA		
Ethyl butyl ketone	50	230	9.0	0.4	0.12	1	20.25
Methyl butyl ketone	100	410	8.6	0.1	0.42	1	20.25
Methyl isobutyl ketone	100	410	8.5	0.2	0.31	1	20.25
Isophorone	25	140	3.4	0.4	0.02	5	20.25
Methyl n-amyl ketone	100	465	8.6	0.3	0.14	1	9.75
Methyl n-propyl ketone	200	700	8.5	0.1	0.23	1	5.25

2. Current Monitoring

No organized monitoring of the ketones in air, water, or soil has been reported in the available literature. Recent reports on their observation in the environment have usually been on grab samples. Table 44 summarizes recent studies which have reported ketones in the environment. Except for the study by Corwin (1969), the ketones were identified among several organic components within the sample and not quantified.

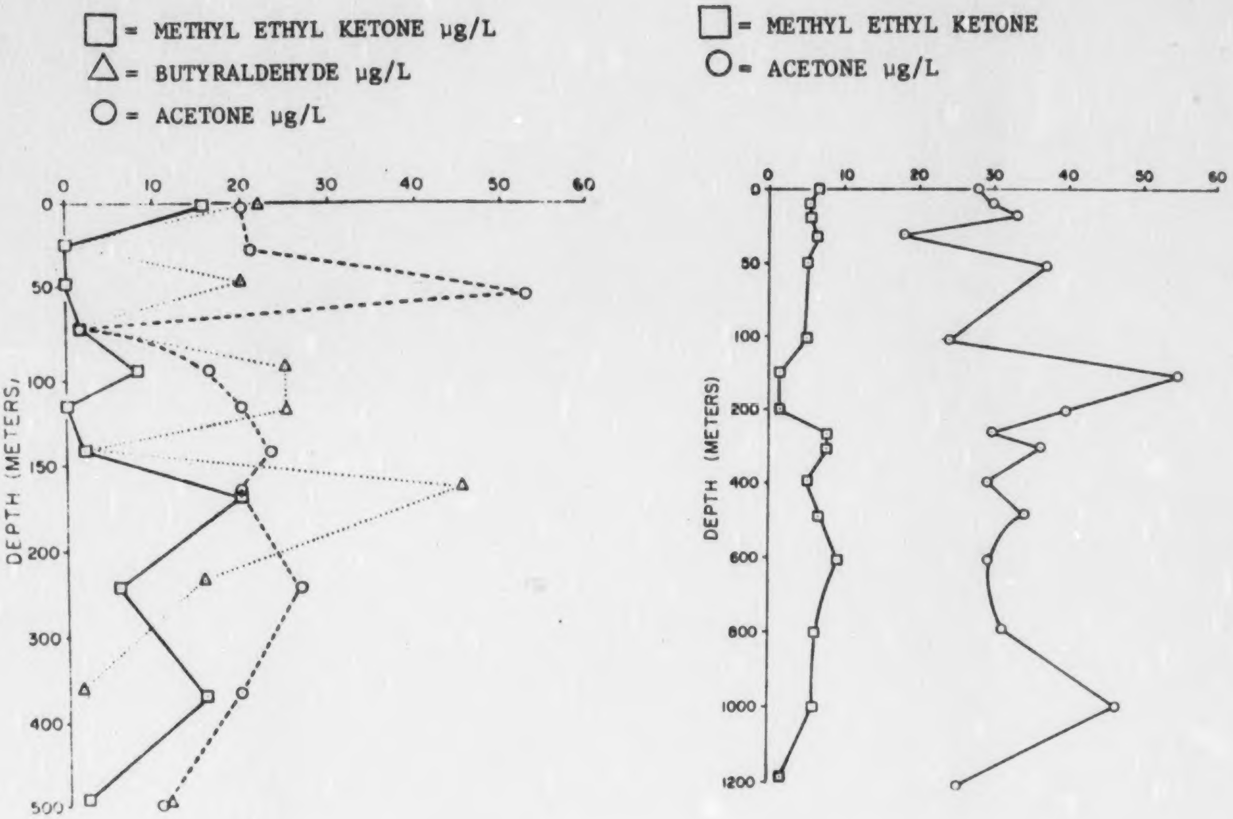
While Corwin (1969) observed variations in ketone concentration (MEK and acetone) between the two sampling locations (one each in the Straits of Florida and the Mediterranean Sea) and between depths of sample collection at each location (see Figure 22), he offers no explanation of the data other than to suggest that the variations could be related to the biota.

Except for the two studies reporting ketones in drinking water (Anon., 1972; Abrams et al., 1975), the remaining ketone samples were from industrial waste streams. The contamination sources for the ketones that were detected in drinking water were not identified.

The apparent minor interest in data on ambient environmental ketone concentrations is perhaps attributed in part to the knowledge that they are present in small quantities in food and throughout the environment, and that analysis of the low concentrations is rather costly. While the ketones do participate in photochemical smog production, at their ambient concentrations their contributions are relatively minor when compared to other hydrocarbons such as olefins and aldehydes (Altshuller, 1966; Altshuller and Bufalini, 1971).

Table 44. Monitoring Data for Selected Ketones

Reference	Source	Ketone	Concentration	Remarks
Alford (1975)	Aquifer, New Castle County, Del.	Diacetone alcohol	2.9 mg/ml	Landfill monitoring well
Corwin (1969)	Sea water, Straits of Florida Sea water, Mediterranean Sea	Methyl ethyl ketone Methyl ethyl ketone	0 - 20 μg/ℓ 0 - 10 μg/ℓ	See Figure 22 See Figure 22
Keith (1974)	Petrochemical plant waste water Calcasieu River, Louisiana	Diacetone alcohol and Acetophenone		Petrochemical company waste stream
Anon. (1972)	Raw and finished, potable waters and industrial waste waters, Mississippi River, Louisiana	Acetophenone, Acetone, and Methyl ethyl ketone		
Webb _et al_. (1973)	Chlorinated paraffin plant's lagoon	Acetophenone		
EPA (1975) Junk and Stanley (1975)	Drinking water and river water	Acetone Acetophenone Isophorone Methyl isobutyl ketone Methyl ethyl ketone Methyl _n_-propyl ketone		
Abrams _et al_. (1975)	Landfill leachate	Acetophenone		
Smoyer _et al_. (1971)	Ambient air near chemical reclamation plant in Maryland	Methyl ethyl ketone	94 ppm	
Grob and Grob (1971)	Ambient air in Zurich, Switzerland	Acetophenone		



a) Sampled at the Straits of Florida

b) Sampled at the Eastern Mediterranean

Figure 22. Distribution, by Depth, of Volatile Organic Compounds in Sea Water (Corwin, 1969)

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III. Health and Environmental Effects

A. Environmental Effects

1. Persistence

a. Biological Degradation, Organisms, and Products

The biological occurrence of aliphatic methyl ketones (see Forney and Markovetz, 1971) coupled with the fact that significant accumulation of these compounds in the biosphere has not been noted, indicates that a recycling of these organic molecules is occurring. The experimental evidence substantiating the rapid removal of ketonic compounds in the environment is meager. The reported studies have mainly considered the degradation and degradation mechanisms in pure cultures of microorganisms. A number of these studies have been oriented towards understanding the mechanism of n-alkane oxidation by microorganisms where methyl ketones are intermediate products. For example, butanone, pentanone, and hexanone were reported to be produced from the respective alkanes by Mycobacterium smegmatis (Lukins and Foster, 1963).

The bulk of the fate-related information available in the literature is for saturated aliphatic ketones (generally C_3 - C_{13}). A few alicyclic ketones have also been studied for their susceptibility to biodegradation. It was further noted from the literature that although microorganisms from a variety of sources (soil, water, activated sludge, etc), have been used in degradation studies; quite often the conditions simulate only the aqueous environment. The salient features of the reported studies on microbial breakdown of ketones are summarized in Table 45.

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Table 45. Summary of the Studies Dealing with Biodegradability of Ketones

Reference	Test Chemical	Concentration Used	Source of Microorganisms	Environmental Conditions Used During the Test	Duration of the Test	Criteria for Test Chemical Alteration
Levine and Krampitz (1952)	Acetone	2 g/liter	*Corynebacterium sp.* enriched from soil	Aqueous (representing high cell concentration)	60 min.	Oxygen uptake determined manometrically
Mills and Stack (1954)	Acetone Diethyl ketone Methyl isobutyl ketone Methyl *n*-amyl ketone Methyl phenyl ketone	50-1000 ppm	Non-flocculent seed developed from settled sewage	Aqueous	10 days	Biological oxygen demand
Goudy *et al* (1963)	Acetone Butanone	1 g/liter as COD	Sewage feed	Activated sludge system (using synthetic waste containing ketones as the sole source of organic carbon)	8 hours	COD measurements
Lukins and Foster (1963)	Methyl *n*-alkyl ketones (C_3-C_{13}) 2,4-Pentadione 3-Heptanone 4-Heptanone Acetophenone	0.2% v/v	Pure cultures of *Mycobacterium smegmatis* 422, and a *Corynebacterium* sp. isolated from alkane enrichment	Aqueous (representing high cell concentration)	30 min.	Oxygen uptake in Warburg respirometer, growth
Marion and Malaney (1963)	Methyl *n*-alkyl ketones (C_3 - C_9) 3-Methyl 2-butanone 3-Heptanone 2-Tridecanone	500 mg/liter	Stock culture of *Alcaligenes faecalis* (a member of the activated sludge flora)	Aqueous (representing high cell concentration)	168 - 192 hours	Oxygen uptake in Warburg constant volume respirometer
Buzzell *et al* (1968)	Acetone 2-Butanone	10 mg/l	Sewage seed	Aqueous	20 days	Oxygen utilization, bacterial population changes, carbon removal
Lowery *et al* (1968)	Methyl *n*-alkyl ketones (C_4-C_7) 3-Pentanone 4-Methyl-2-pentanone 4-Heptanone Cyclohexanone	0.05 ml ketone/20 ml growth medium	Stock cultures of yeast - *Candida lipolytica*, *C. pulcherrima*, *Candida* sp. T13, *Rhodotorula glutinis*	Aqueous	23 days	Growth
Perry (1968)	Methyl *n*-alkyl ketones (C_3-C_8)	4-2 mM	Brevibacterium sp. isolated from soil by enrichment with 2-methylbutane	Aqueous (representing high cell concentration)	90 min.	Oxygen uptake in Warburg respirometer
Buzzell *et al* (1969)	Acetone 2-Butanone	180 mg/l as carbon	Freeze dried sludge	Activated sludge system	12 hours	Oxygen uptake in Warburg, soluble carbon removal
Norris and Trudgill (1971)	Cyclohexanone	Not stated	*Nocardia globerula* CL1 isolated by soil enrichment with cyclohexane as the carbon source	Aqueous (representing high cell concentration)	Not stated	Oxygen uptake in Warburg manometer
Murray *et al* (1974)	Cyclohexanone	0.1% (v/v) in growth studies; 0.5 µM in respiration studies	*Nocardia* sp. isolated by soil enrichment with cyclohexanone as the carbon source	Aqueous (representing high cell concentration)	7 days for growth	Growth; oxygen uptake by both manometric and polarographic technique
Phillips and Perry (1974)	2-Butanone	Not stated	Pure cultures of *Mycobacterium vaccae*	Aqueous	72 hours	Growth
Metabolism by photosynthetic bacteria						
Siegel (1954); Siegel and Smith (1955); Siegel (1957)	Acetone	15-30 µM during metabolic studies; 0.2% during growth	Stock cultures of photosynthetic bacterium *Rhodopseudomonas gelatinosa*	Up to 6 hours	Aqueous	Conversion to cellular intermediates, ^{14}C-assay

The available information has been organized into three sections: (1) pure culture studies, (2) mixed culture studies, and (3) activated sludge systems. The information pertinent to each of these categories is reviewed below.

(1) Biodegradation by Pure Cultures of Microorganisms

Pure culture studies dealing with the metabolism of ketones by heterotrophic (those bacteria which use organic carbon for growth) and photosynthetic bacteria (utilizing light as the source of energy), and fungi have been reported. The heterotrophic microorganisms are perhaps of major significance in removal of organic contaminants from the environment, and, therefore, these studies will receive more emphasis.

(a) Biodegradation by Heterotrophic Bacteria

(i) Methyl *n*-alkyl ketones

Isolation of the bacteria capable of metabolizing methyl *n*-alkyl ketones has been reported by a number of researchers. Among the various ketones, acetone has been investigated most extensively. As early as 1923, Supniewski (1923) reported that *Bacillius pyocyaneous* would grow in a medium containing 0.23% acetone, and that it produced acetic and formic acids as end products of growth. Levine and Krampitz (1952) failed to isolate an acetone oxidizing organism from soil using an enrichment medium consisting solely of inorganic salts and acetone. Upon supplementing the enrichment medium with yeast extract, a *Corynebacterium* sp. was isolated, which was able to oxidize acetone. The ability of the organism to oxidize acetone was an adaptive process, and required growth of the organism in the presence of acetone. Lukins and Foster (1963) reported isolation of 4 bacterial strains (tentatively named as MB_5, MB_2, MA_0 and MC_5) from soil and mud, which were able to use 2-butanone as a carbon source. No information regarding the rate of growth and/or the rapidity of the breakdown by the isolated organisms was revealed in this study. Pure cultures of Alcaligenes faecalis, an organism which has been identified as a member of the activated sludge flora, were reported to be able to oxidize acetone and heptanone after a lag period of about 5 days (Marion and Malaney, 1963). Under similar conditions, other methyl n-alkyl ketones tested (2-butanone, 3-methyl-2-butanone, 2-pentanone, 2-octanone and 2-nonanone) appeared to be resistant to oxidation (Figure 23). The interpretation of the experimental data is complicated by the fact that the cells consumed oxygen in the absence of the test chemical at high rates. The presence of the endogenous oxidizable substrate may have prevented the adaptive synthesis of the enzymes responsible for the breakdown of ketones. An inhibition of the adaptive synthesis of the acetone oxidizing system in Corynebacterium sp. by increase in the concentration of yeast extract in the medium has been noted by Levine and Krampitz (1952). The problem of interpreting the data (Marion and Malaney, 1963) is further magnified due to possible changes in the endogenous oxygen uptake due to the presence of the added ketones.

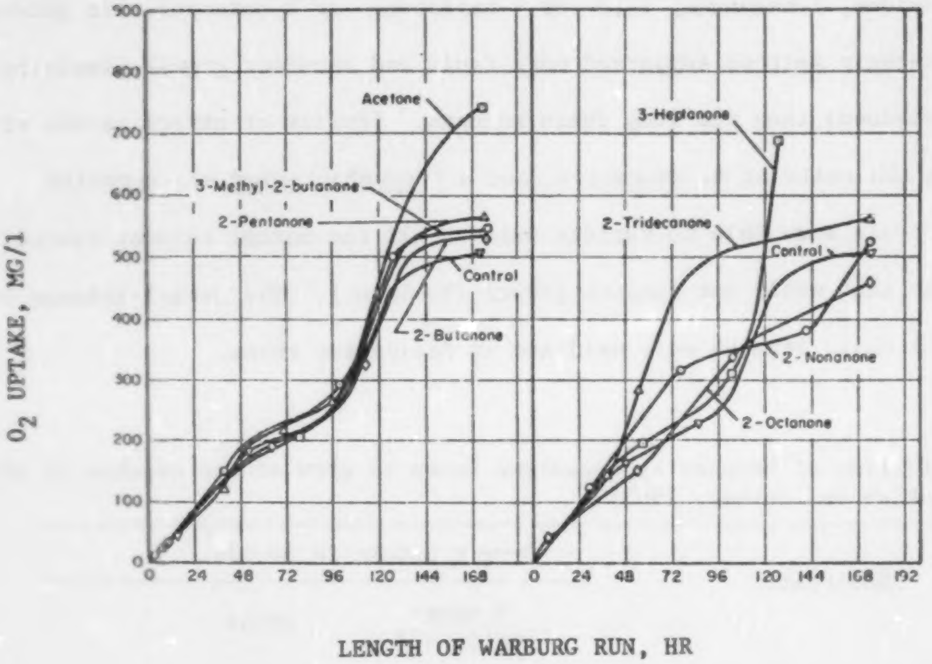

Figure 23. Oxidation of ketones by *Alcaligenes* *faecalis*. (Marion & Malaney, 1963)

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Methyl *n*-alkyl ketones have been reported to be involved in alkane oxidation by microorganisms (Forney and Markovetz, 1971; Lukins and Foster, 1963). From this, it appears likely that the cells grown on alkanes might be simultaneously adapted to grow and/or oxidize corresponding methyl ketones. A number of studies have been reported which deal with the metabolism of methyl ketones by alkane utilizing microorganisms. Lukins and Foster (1963) reported that the strains of *Mycobacteria* (*M*. *smegmatis* 422, *M*. *rhodochrous* 382, and *M*. *fortuitum* 389), when grown at the expense of alkanes, were also able to grow on acetone, 2-butanone, and 2-pentanone as a sole source of carbon. In comparable tests, none of the organisms grew on 3-pentanone, 2,4-pentadione, 2-hexanone, 2-,3- or 4-heptanone, or 2-octanone. In general, the short-chain ketones supported more rapid and abundant growth (implying rapid breakdown) than the long chain ketones. Studies of oxygen uptake with propane grown cells of M. smegmatis, and a Corynebacterium sp. revealed that the cells were able to rapidly oxidize all the methyl ketones tested, even those that would not support growth (Table 46). The methyl ketones with increasing chain lengths were oxidized at decreasing rates.

Table 46. Oxidation of ketones by organisms known to grow at the expense of alkanes (Lukins and Foster, 1963)

Substrate	Oxygen uptake in 30 min.	
	M. smegmatis 422	OS15*
	μliters	μliters
None	13	14
Acetone	244	325
2-Butanone	196	266
2-Pentanone	180	
3-Pentanone	176	
2,4-Pentandione	92	
2-Hexanone	217	183
3-Heptanone	98	
4-Heptanone	108	
2-Octanone	116	78
2-Undecanone	89	52
2-Tridecanone	109	78
Acetophenone	52	

* A Corynebacterium sp. isolated from propane enrichment cultures.

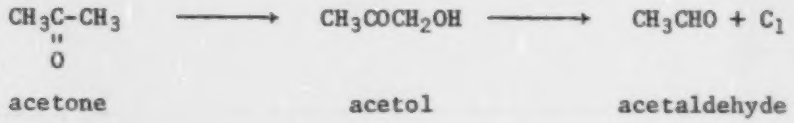
In a similar study, Perry (1968) found that $C_1 - C_8$ alkane grown cells of Brevibacterium strain JOB5 were able to oxidize $C_3 - C_8$ n-alkyl methyl ketones (Table 47). None of the ketones except acetone, however, were able to support growth of the organisms. The susceptibility to oxidation in general, increased with an increase in the chain length of the ketones tested. This is contrary to the findings of Lukin and Foster (1963), with Mycobacterium sp. (see above).

Table 47. Oxidation of n-Methyl Ketones by Brevibacterium Strain JOB5 Cells Grown on Paraffinic Hydrocarbons[a] (Perry, 1968)

Respirometer substrate	Growth substrate							
	Methane	Ethane	Propane	Butane	Pentane	Hexane	Heptane	Octane
Acetone	10	2	21	13	59	1	0	0
Butanone	56	26	39	85	91	3	9	14
Pentanone	48	36	25	80	66	23	22	17
Hexanone	25	17	9	208	73	31	60	20
Heptanone	88	63	99	204	150	97	77	47
Octanone	98	75	83	90	114	67	87	75

[a] Total µliters O_2 uptake in 90 minutes.

Information on the pathways of breakdown of ketones in microbial systems is meager. Short chain methyl n-alkyl ketones have received considerably more attention than other compounds. Supniewski (1923) notes that Bacillus pyocyaneus grown on acetone as the sole carbon source, produced acetic and formic acids as end products. From the ability of acetone grown cells of a soil Corynebacterium to oxidize acetol (1-hydroxy-propan-2-one) and acetaldehyde, Levine and Krampitz (1952) concluded that these compounds may be intermediates in the pathway of acetone oxidation. The author proposed that the oxidation of acetone gives rise to acetol, which undergoes cleavage to yield acetaldehyde and a one-carbon unit as follows:



$$\underset{\text{acetone}}{CH_3\underset{\overset{\|}{O}}{C}-CH_3} \longrightarrow \underset{\text{acetol}}{CH_3COCH_2OH} \longrightarrow \underset{\text{acetaldehyde}}{CH_3CHO + C_1}$$

Oxidation was further confirmed by the results of the studies utilizing ^{14}C-carbonyl labelled acetone. Acetol was also isolated and characterized as an oxidation product of acetone by Mycobacterium smegmatis (Lukins and Foster, 1963). Presumptive evidence was also obtained for the formation of a corresponding hydroxy-substituted intermediate (suspected to be 1-hydroxy-2-butanone) during the bacterial oxidation of butanone. Ethyl acetate and ethanol were reported to be intermediates in 2-butanone catabolism by a soil Nocardia (referred to as LSU 169) (Eubanks, 1973). It was proposed that the bacterium converted 2-butanone to ethyl-acetate which was subsequently hydrolyzed to ethanol and acetate.

The first report of the isolation and characterization of an oxidative intermediate from the metabolism of any methyl ketone other than acetone was provided by Forney and his coworkers (Forney *et al*., 1967; Forney and Markovetz, 1968). In the culture fluid of a *Pseudomonas multivorans* incubated with 2-tridecanone, the authors identified 2-tridecanol, 1-undecanol, 1-decanol and undecanoic acid. In subsequent studies, a new intermediate, undecyl acetate, was identified. Based on their findings, the authors proposed the pathways illustrated in Figure 24, for the oxidation of 2-tridecanone; the pathway provides for conversion of the substrate to acetate, a common central metabolite in cellular metabolism.

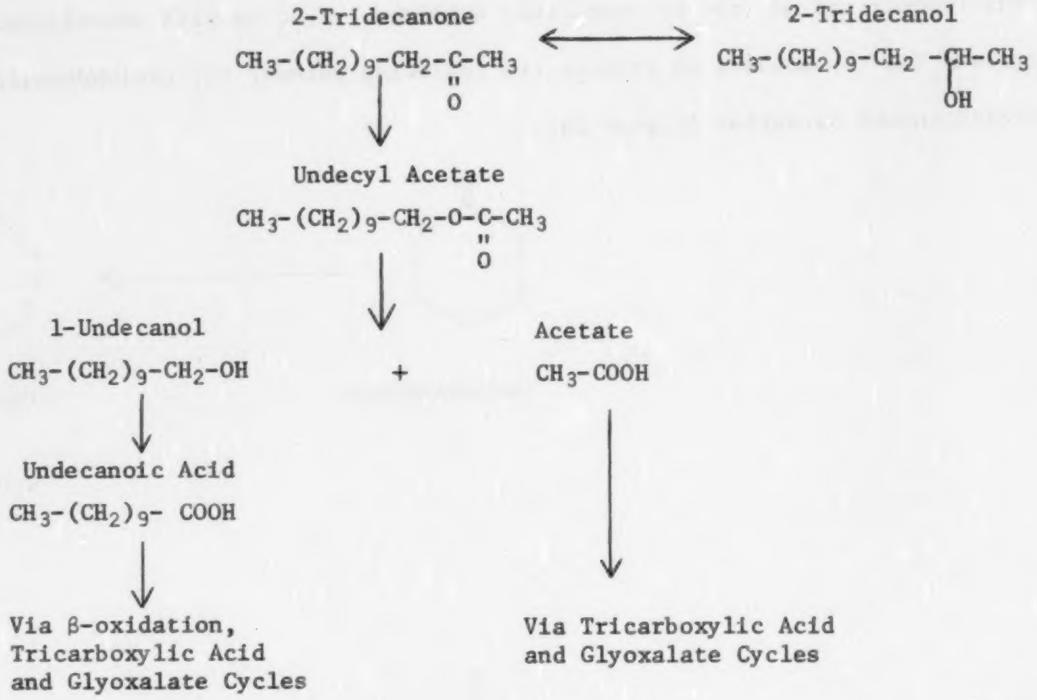

2-Tridecanone
CH3-(CH2)9-CH2-C-CH3
O
2-Tridecanol
CH3-(CH2)9-CH2 -CH-CH3
OH
Undecyl Acetate
CH3-(CH2)9-CH2-O-C-CH3
O
1-Undecanol
CH3-(CH2)9-CH2-OH
+
Acetate
CH3-COOH
Undecanoic Acid
CH3-(CH2)9- COOH
Via β-oxidation, Tricarboxylic Acid and Glyoxalate Cycles
Via Tricarboxylic Acid and Glyoxalate Cycles

Figure 24. Proposed Pathway for Complete Degradation of 2-Tridecanone by Two Aerobic Pseudomonads (Forney and Markovetz, 1968)

Although the pathway of breakdown of methyl *n*-alkyl ketones has been investigated in some depth in pure cultures of microorganisms, nothing is known about the environmental fate and the pathways of breakdown in the environment.

(ii) Cyclohexanone

Norris and Trudgill (1971) reported that Nocardia globerula enriched on cyclohexanol was able to oxidize cyclohexanone at rates very similar to that for cyclohexanol. Each mole of cyclohexanone was oxidized with the consumption of 1.65 mole of oxygen. Theoretically, 8 moles of oxygen are needed for complete oxidation of one mole of cyclohexanone. This suggests accumulation of a less oxidized intermediate. Alternatively, some of the cyclohexanone carbon may be converted to cellular constituents and may not be completely oxidized. Studies with subcellular systems led the authors to propose the following pathway for cyclohexanol/cyclohexanone oxidation (Figure 25).

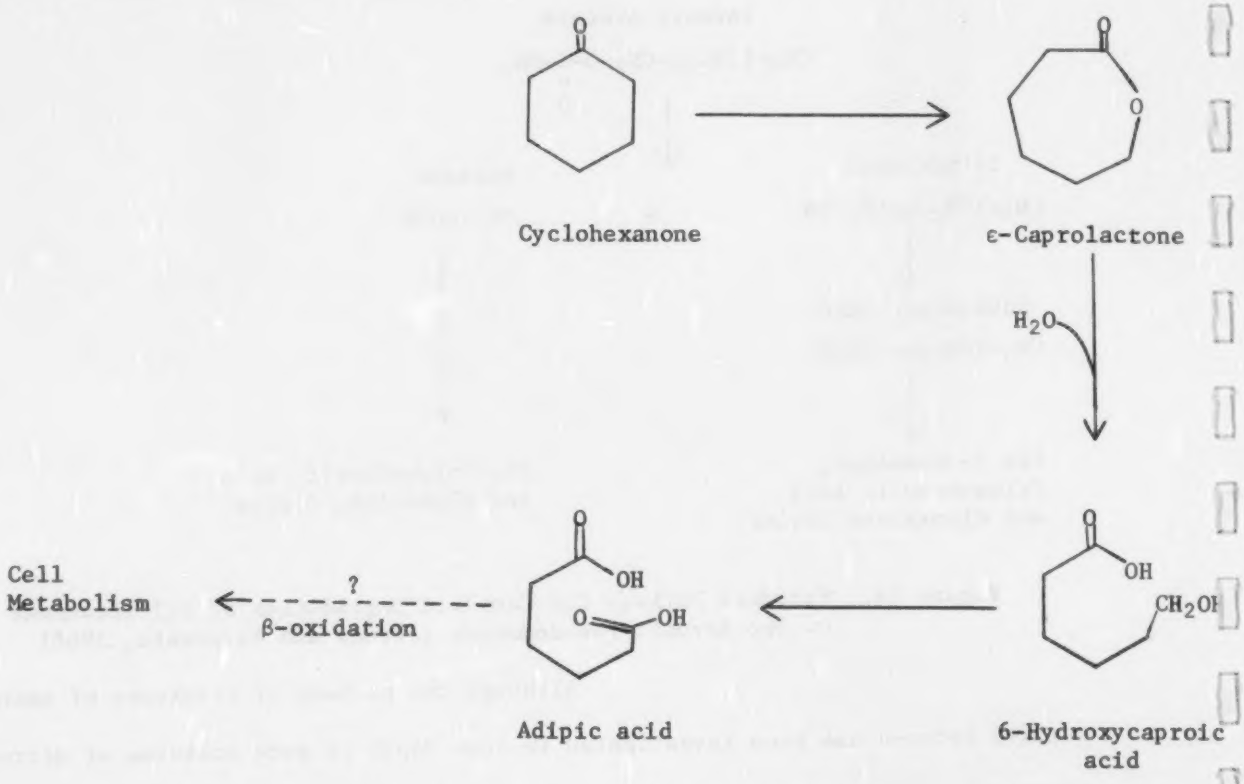

Cyclohexanone
ε-Caprolactone
H2O
6-Hydroxycaproic acid
Adipic acid
?
β-oxidation
Cell Metabolism
O
OH
CH2OH

Figure 25. Reaction Sequence for the Oxidation of Cyclohexanone by Nocardia globerula CL1, (Modified from Norris and Trudgill, 1971)

A species of Nocardia, which used cyclohexanone as sole source of carbon for growth, was isolated from soil by Murray and coworkers (1974). Non-proliferating cells of this organism were able to rapidly oxidize cyclohexanone. Cyclohexane-grown cells exhibited no growth on the related compound, cyclohexane-1,2-dione. Gas chromatographic analysis of the supernatant from cultures growing on cyclohexanone revealed that a possible intermediate in the degradation was 2-hydroxycyclohexan-1-one. This is a different mechanism than the one proposed by Norris and Trudgill (1971), which involved the formation of a lactone (Figure 25).

(b) Biotransformation Catalyzed by Photosynthetic Bacteria

Many photosynthetic bacteria are able to metabolize organic substrates photosynthetically, and also aerobically in darkness. A number of researchers have investigated the metabolism of acetone by photosynthetic microorganisms. The reported studies have, however, been oriented towards understanding the mechanism of substrate assimilation in relation to bacterial photosynthesis, rather than the environmental fate of methyl ketones. Moreover, it is unclear at the present time as to what role, if any, photosynthetic microorganisms play in the breakdown of organic contaminants in the environment. Photosynthetic bacteria are generally found in places where oxygen is deficient, but light is not a limiting factor. Such areas are sediments of ponds, estuarine sediments, narrow banks in the lakes, and open ocean where oxygen has been depleted and there is still a low light intensity. It is likely that in these environmental mediums, photosynthetic bacteria may have some role in metabolizing ketones.

Siegel (1954) reported the photosynthetic conversion of acetone to acetate by the photosynthetic bacterium Rhodopseudomonas gelatinosa grown in light in the presence of acetone. Seigel and Smith (1955) later investigated the dark aerobic metabolism of acetone by R. gelatinosa and found that acetone underwent direct carboxylation with CO_2 to form acetoacetate, which is the precursor of acetate. These investigations further indicated that the same metabolic pathway is followed in the dark aerobic metabolism of acetone as in its photosynthetic metabolism, and that energy must be provided at discrete points in the pathways. The available energy is used for the carboxylation of acetone to form acetoacetate, or for assimilation of acetate, a low molecular weight cellular intermediate, into cell material. On the basis of their experimental findings, Siegel and coworkers proposed the following pathway (Figure 26) for metabolism of acetone in the photosynthetic bacterium. Other ketones could perhaps also be attacked by photosynthetic bacteria; however, no experimental data is available at the present time to support this possibility.

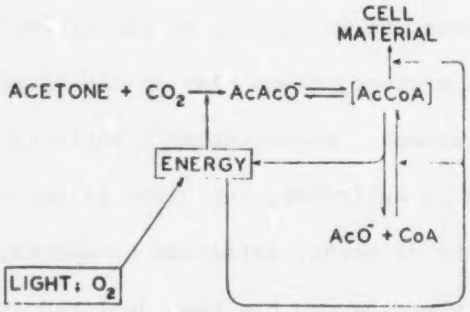


Figure 26. Photosynthetic and Aerobic Metabolism of Acetone in R. gelatinosa (Siegel, 1957)

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(c) Biodegradation of Ketones by Fungi

Hopkins and Chibnall (1932) established that *Aspergillus versicolor*, which grew on long-chain paraffins, also grew on related methyl ketones. Lowery and coworkers (1968) surveyed several species of yeasts for their ability to utilize various ketones as growth substrates. The authors found that several species of genus *Candida* were able to utilize some of the methyl ketones tested (Table 48). It was concluded that 2-hexanone and 2-heptanone were most readily utilized. The data further indicated that shifting the position of the carbonyl groups, methyl substitution, cyclization, unsaturation, and the introduction of a second carbonyl group all rendered these ketones unsuitable for growth.

Table 48. Growth of Yeasts on Individual Ketone Substrates[1] (Lowery *et al*, 1968)

Substrate[2]	Microorganisms[3]				
	Candida lipolytica (8661)	*Candida pulcherrima* (Merck)	*Candida* sp. T 13	*Rhodotorula glutinis* (U. of Cal)	*Rhodotorula glutinis* (145 H)
2-Butanone	-	-	±	-	
2-Pentanone	-	-	3 +	±	±
3-Pentanone	-	-	-	±	±
4-Methyl-2-pentanone	-	-	-	±	±
2-Hexanone	±	4 +	4 +	-	-
Cyclohexanone	-	-	-	±	±
2-Heptanone	2 +	4 +	4 +	-	-
4-Heptanone	-	-	-	±	±
2-Undecanone	2 +	-	-	-	-

[1] No growth (-); trace of growth (±); growth (2 +); good growth (3 +); and abundant growth (4 +).

[2] None of the yeasts tested grew on the following ketones: acetone, 2,3-pentanedione, 2,4-pentanedione, 3-methyl-2-pentanone, 5-methyl-2-hexanone, 5-hexene-2-one, 3-heptanone, 3-methyl-2-heptanone, 2,3-heptanedione, 2-octanone, 2-nonanone, 2-decanone and pinacolone.

[3] *Candida brumptii*, *Candida guillermondii* and *Candida* sp. T 16 were not able to utilize any of the above ketones as growth substrate.

(2) Biodegradation by Mixed Cultures

Relatively little information is available concerning the biodegradability of ketones in the presence of mixed cultures of microorganisms. Mills and Stack (1954) have reported the results of a 10-day BOD test with methyl n-alkyl ketones. These investigators inoculated the dilution bottles with dispersed seed (non-flocculent growth, see Heukelekian, 1949), developed from settled sewage and acclimated to an organic mixture that approximated their company's plant process effluent. The simulated process effluent was also used as the dilution water in this study; the BOD equivalent for the ketones were calculated from the difference between the BOD of the process effluent, and the process effluent plus ketone. A shortcoming of this approach is that the presence of ketones may cause considerable change in the oxidation of the process effluent chemicals; and in that case, the subtraction of the BOD of the process effluent will not represent the oxygen used for biodegradation of the ketones.

As shown in Table 49, the ketones investigated (acetone, 2-butanone, methyl isobutyl ketone, methyl n-amyl ketone, and acetophenone) were susceptible to oxidation. The 10 day BOD test was greatest for acetone, the oxygen depletion decreased with an increase in chain length. A comparison of the amount of oxygen consumed per mole of substrate with the calculated theoretical oxygen demand revealed that the test ketones were not completely mineralized. However, a low oxygen to substrate ratio could also be expected if part of ketonic carbon was assimilated by the cell and converted to cell constituents and intermediates which are less oxidized than the terminal oxidation product - CO_2. Data is not available to distinguish between the two explanations.

Table 49. Results of a 10-Day BOD Test With Ketones (Mills and Stack, 1954)

Substrate	ppm Oxygen Depletion in 10 days (Substrate Concn., 1000 ppm)	Equivalents, Moles of Oxygen/ Mole of Substrate	
		Observed	Theoretical (for Complete Oxidation)
Acetone	1030	2.17	4
Diethyl ketone	820	2.7	7
Methyl isobutyl ketone	600	1.9	8.5
Methyl _n_-amyl ketone (2-heptanone)	360	1.8	10
Methyl phenyl ketone (Acetophenone)	240	5.25	9.5

In a 20 day BOD test, Buzzell and coworkers (1968) found that both acetone and methyl ethyl ketone (2-butanone) were extensively oxidized (Figure 27). Nitrification was not detected until the 12th day of the study, suggesting little error in the oxygen uptake data due to non-carbonaceous oxygen consumption. The results of the chemical oxygen demand and total organic carbon in the same samples closely corroborated the results of the oxygen utilization data. The increase in microbial population concurrent with the oxidation of ketones further supports the view that the test ketones were metabolized by microorganisms.

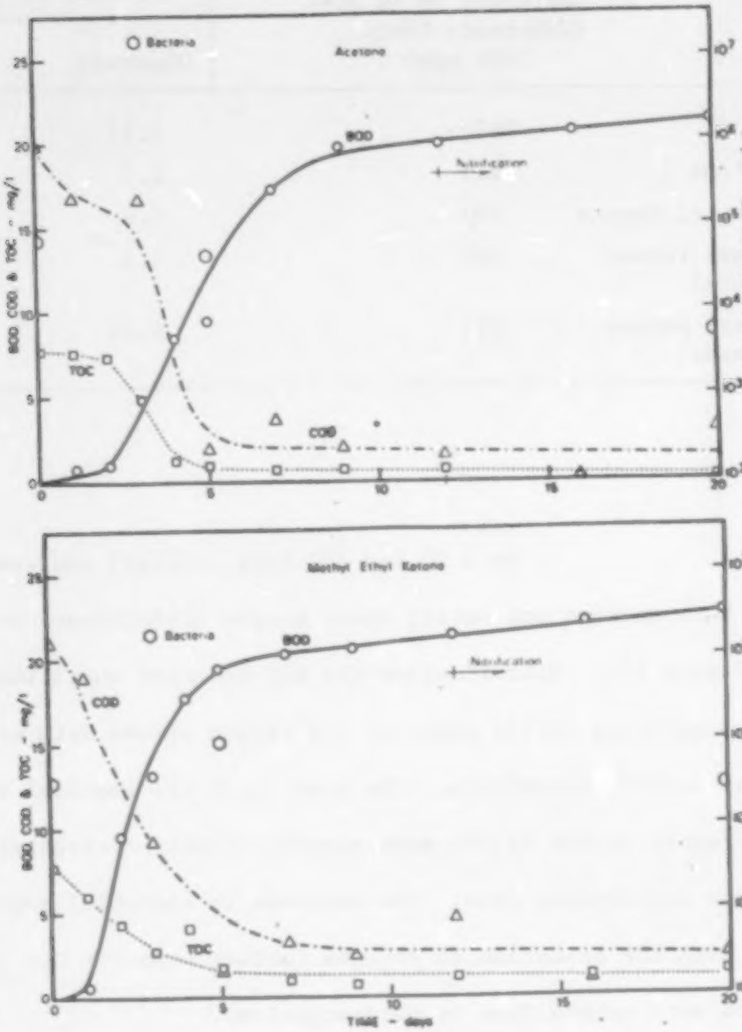

Figure 27. Results of a 20-Day Biodegradability Test With Acetone and Methyl Ethyl Ketone (Buzzell _et_ _al_., 1968)

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(3) Biodegradation in Activated Sludge System

In an effort to investigate the kinetics of volatile substrate removal in activated sludge systems, Gaudi et al. (1963) employed acetone and butanone as model substrates. In an activated sludge system, a volatile organic substrate is removed by dual mechanisms - physical stripping and biological metabolism. The rate of biological removal of ketones was determined in a Warburg apparatus. At the substrate concentration and temperature employed in the study, the authors confirmed that the losses due to physical stripping were not a serious concern in the Warburg apparatus, and that the removal would truly reflect the biological metabolism. The rates of loss due to physical stripping were separately determined and the two kinetic constants were integrated to obtain a combined kinetic equation.

Mixed liquor taken from the activated sludge system developed from a sewage seed and synthetic waste containing ketones served as the biological material in the Warburg study. The loss of ketones was followed by determining COD at various intervals. The results of this study are depicted in Table 50. Nearly 40-60% loss of ketones was noted after 8 hours. Unfortunately, the experiments were terminated at 8 hours (perhaps due to depletion of all the oxygen) and, therefore, it is unclear if complete removal of these compounds would have occurred. The rate of loss of the ketones was reported to be a zero-order kinetic process (with acetone, however, the data could also be fitted to first-order kinetics). The uptake of oxygen linked to the oxidation of ketones, and the increase in biological solids in the system (apparently at the expense of the ketones), provide further support for the susceptibility of these compounds to microbial attack.

Table 50. Biological Removal of Ketones in Warburg Apparatus (Gaudi *et al*, 1963)

Substrate	Substrate Concentration mg/l as COD	Biological Velocity Constant*		Increase in Biological Solids in 8 Hours mg/liter	Oxygen Uptake/ mg solids**
		First Order Kinetics hr^{-1}	Zero Order Kinetics mg/ℓ/hr		
Acetone	1000	0.0261-0.0329	50-60	66-125	0.0356-0.0962
Butanone	1000		62.5-110	Lower than initial concentration -63	0.0307-0.0397

* Where the data could be fitted to both first and zero order kinetics, both velocity constants are given.

** Accumulated oxygen uptake in two hours (units unclear) divided by initial solids concentration (mgs).

Buzzell *et al*. (1969) studied the biodegradability of acetone and 2-butanone in a Warburg respirometer, and parallel shake culture studies under conditions which simulated slug loading of an activated sludge process. Standardized activated sludge culture, which had been preserved by freeze drying and rejuvenated prior to use, was used to inoculate the flasks. The mixed liquor volatile suspended solids (MLVSS) at the start were 2500 mg/ℓ;

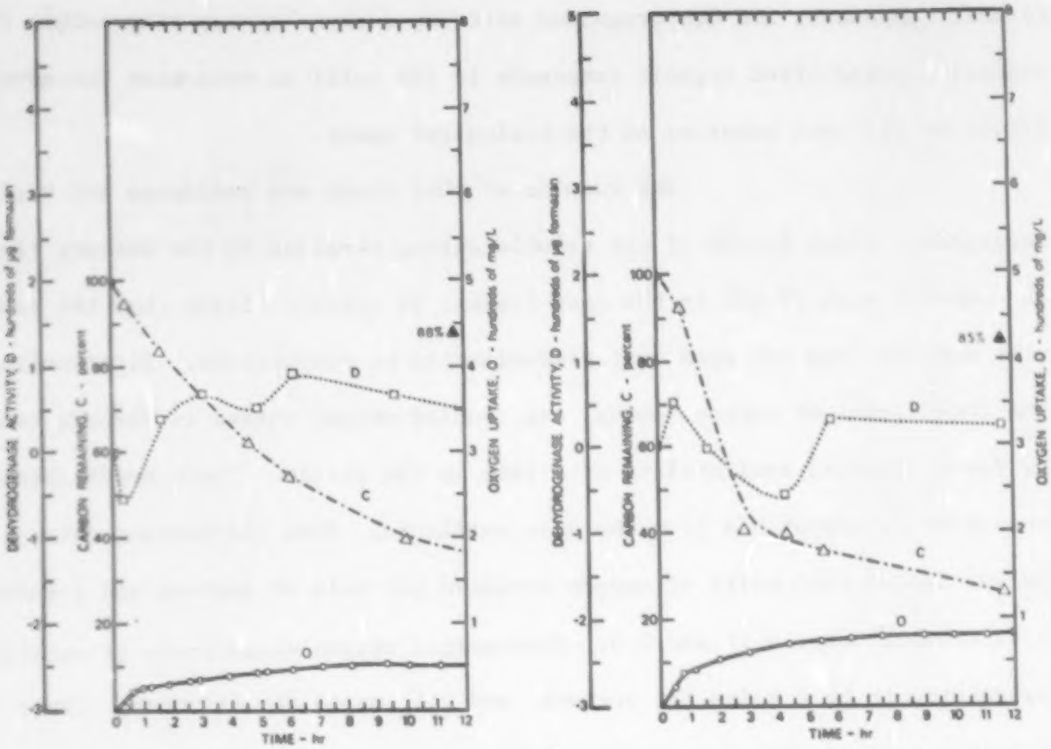

Figure 28. Behavior of Acetone and 2-Butanone in the Activated Sludge Environment (Buzzell _et_ _al_., 1969)

Warburg Respirometer Studies

O: Oxygen utilization
▲: Percentage of the initial soluble carbon remaining

Parallel Shake Culture Studies

C: Soluble organic carbon removal
D: Changes in dehydrogenase enzyme activity

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the organic chemical was at 180 mg/ℓ as carbon. The authors measured oxygen utilization and soluble carbon removal to assess the biodegradability of the ketonic compounds, and dehydrogenase activity (enzyme system responsible for oxidizing unspecified organic compounds in the cell) to determine the adverse effect of the test material on the biological agent.

The results of this study are confusing and hard to interpret. Since 85-88% of the soluble carbon remained in the Warburg flask, as compared with 27-35% in the open flasks, it appears likely that the compounds were removed from the open unit predominantly by evaporation. Alternatively, the lower level of carbon removal and coupled oxygen uptake in Warburg could be due to limited availability of oxygen in the system. These possibilities cannot be distinguished from the data available. From the Warburg data, it can be calculated that moles of oxygen consumed per mole of acetone and 2-butanone are, respectively, 4.11 and 4.9. Theoretical oxygen demand/mole of substrate is calculated to be 4 moles for acetone, and 5.5. moles for butanone. These findings suggest that the soluble carbon removed in the Warburg study (12-15%) was completely mineralized by microbial action.

(4) Probable Environmental Fate of Ketones

In studying biodegradation of ketones, researchers have frequently utilized pure cultures of microorganisms. The pure culture studies in general reveal very little about the environmental fate of a chemical. In that respect, they have very limited application. However, upon considering a number of points such as the relative ease by which an organism can be isolated which metabolizes the chemical, how extensively and rapidly the chemical is degraded by the isolated organism, whether acclimation is required for degradation to occur, some insight into the environmental fate of the chemical can be achieved. In this section, an attempt has been made to infer from the reported studies, the probable fate of ketones under environmental conditions.

The projected environmental fate of ketones is summarized in Table 51. As can be seen, information is available for most methyl n-alkyl ketones, some methyl substituted ketones (4-methyl-2-pentanone, 3-methyl butanone), and certain alicyclic ketones. Other commercially important branched chain ketones (e.g., diisopropyl, diisobutyl, methyl isobutyl, methyl isoamyl, trimethyl nonanone, mesityl oxide, and diacetone alcohol) have not been investigated for their susceptibility to microbial attack.

The available data suggests that most methyl n-alkyl ketones are susceptible to microbial degradation. Lower chain ketones appear more easily attacked. Methyl substitution (branching), unsaturation, and introduction of a second carbonyl group tend to make the resulting compound harder to degrade. Alicyclic ketones (e.g., cyclohexanone) appear to be also

Table 51. Biodegradability of Ketonic Solvents - Summary of Information

Compounds Tested	Type of Test	Probable Fate in the Environment
2-Butanone	P, AS, M	+ +
3-Methylbutanone	P	±
2-Pentanone	P	+ +
3-Pentanone	P	±
4-Methyl-2-pentanone	P, M	±
2,4-Pentadione	P	±
2-Hexanone	P	+ +
2-Heptanone	P, M	+ +
3-Heptanone	P	+ +
4-Heptanone	P	+
2-Octanone	P	+
Cyclohexanone	P	+ +
Acetophenone	P, M	±

P: Pure culture
M: Mixed culture
AS: Activated sludge system

+ +: Extensive degradation
+: Minor transformation
±: Uncertain

attacked fairly easily by microorganisms and degraded to cellular intermediates. In general, it appears unlikely that ketonic solvents will accumulate in aquatic or soil environment to a considerable extent. However, it is possible that because of their extremely volatile nature, they may escape from soil and/or water and reside predominantly in the atmospheric environment, where little biodegradation generally takes place. Therefore, their ultimate environmental fate will be dependent not only on their susceptibility to microbial attack, but also on the rate of exchange between environmental media, mobility in a particular environment, and photochemical and chemical breakdown in the atmosphere. Furthermore, the media in which ketonic solvents are initially released (Section II-C, p. 92) will have a considerable effect on the overall fate of these chemicals. For example, if they are discharged into sewage treatment plants where biological activity is very high, a substantial quantity may be biodegraded, and loss due to volatility may be small.

b. Chemical Degradation in the Environment

Information on the chemical degradation of the ketones is reviewed in Section I-B-2,3 (see pages 24-38). The ketones are stable to the usual environmental oxidants and are not degraded by hydrolysis. Some of the ketones produced by condensation of acetone (e.g., mesityl oxide and diacetone alcohol), could fragment back to acetone in environments of slightly acidic or alkaline conditions. The ketones which are the subject of this study will also be photochemically degraded to a significant extent (the branch chain ketones are somewhat more susceptible). The overall persistence of ketones in the environment will thus be dependent to a significant extent on their chemical and photochemical breakdown.

2. Environmental Transport - Volatility, Leaching, and Downward Movement

No experimental data has been reported concerning the transport and mobility of ketonic solvents in the environment. The information presented below has been derived largely from the physical and chemical properties of these compounds.

The vapor pressure of a chemical determines, to a great extent, the magnitude of loss of that compound to the atmosphere. The high vapor pressure of ketones (see Table 4), suggests that these compounds are volatile enough to enter and distribute through the atmosphere. The low molecular weight ketones (e.g., methyl ethyl ketone, methyl propyl ketone, etc.) will be lost much more rapidly than higher molecular weight ketones.

Organic chemicals are gradually lost from aqueous solution by codistilling with water; the rate of loss by this mechanism is dependent upon the compounds vapor pressure, water solubility, and adsorption properties (Kenaga, 1972). Mackay and Wolkoff (1973) have developed an equation (see Table 52) for predicting the evaporation rate of slightly soluble organic compounds from water. Using this approach, the half-lives for evaporation of ketonic solvents from aqueous solutions have been calculated and are presented in Table 52. In general, it appears that ketones will not be rapidly lost to the atmosphere from aqueous solutions; this may be attributed to their relatively high water solubility.

The recent studies of Dilling et al. (1975) have raised some question concerning the validity of the approach advanced by Mackay and

Wolkoff (1973) for calculation of evaporation half-lives for chemicals. Dilling et al. (1975) found a discrepancy between experimentally determined half-lives of certain low molecular weight chlorinated hydrocarbons and values calculated according to the equation developed by Mackay and Wolkoff (1973). The authors noted that the experimental values were always much higher than calculated values; furthermore, the seven-fold variation in the calculated values between the compounds predicted to evaporate the most slowly (half-life, 0.34 min) and the most rapidly (half-life, 2.3 min) was not reflected in the experimental values (evaporation half-life range, 21-27 min). In view of this information, it is suggested that the calculated evaporation half-lives be treated as only rough approximations, and be used only to draw general conclusions about the evaporation losses of ketonic solvents.

Table 52. Rate of Evaporation of Ketones From Aqueous Solutions (calculated according to Mackay and Wolkoff, 1973)

Ketone	Vapor Pressure mm Hg at 20°C	Calculated Evaporation Half Life at 20°C* (Hours)
Methyl ethyl ketone	70	138
Methyl propyl ketone	27	48
Methyl isobutyl ketone	15	33
Methyl n-amyl ketone	2	49
Ethyl butyl ketone	4	24.5
Diisobutyl ketone	1	9.1
Mesityl oxide	8	92.7
Cyclohexanone	2	331.2
For Comparison		
Benzene	95.2 (25°C)	0.62 (25°C)
DDT	1×10^{-7} (25°C)	88.8 (25°C)

Data on molecular weight, vapor pressure and solubility obtained from Tables 2, 3 and 4 were used in these calculations..

* at less than saturation concentrations in a square meter of water undergoing constant mixing.

Method of calculation (Mackay and Wolkoff, 1973)

$$\tau \text{ (days)} = \frac{12.48 \quad L\, P_W \quad C_{is}}{E \quad P_{is} \quad M_i}$$

τ = half life of a chemical present at less than saturation

L = depth of water; it is convenient to consider depth of 1 meter (i.e., a total volume of $1m^3$)

P_W = partial pressure of water (23.76 mm of Hg at 25°C)

C_{is} = solubility of compound in water in mg/l

E = evaporation rate of water (2740 g/m^2/day, used by Mackay and Wolkoff, 1973)

P_{is} = vapor pressure of the compound

M_i = molecular weight of the compound

In view of their relatively high water solubility, it appears likely that the ketones lost to the atmosphere due to volatilization, and codistillation with water, will be washed out of the atmosphere with rain. Thus, ketones may reside for extended periods of time in water, and some cycling between air and water is likely.

Volatilization of chemicals from soil and other surfaces depends upon the vapor pressure of the chemical as modified by the adsorptive interactions with the surface (Spencer and Cliath, 1975). Since ketones are very water soluble, they will more likely be contained in soil water and, thus, significant evaporation losses of ketones from soil may occur. The high water solubility will allow the ketones to migrate through soil and eventually make their way to ground water. In general, the physical properties of ketones indicate that they should be fairly mobile in the environment.

3. Bioaccumulation

Bioaccumulation (also referred to as bioconcentration) refers to concentration of a compound by an organism from the surrounding environment by various processes, including absorption, adsorption, ingestion, etc. Experimental data concerning bioaccumulation potential of ketones is not available in the literature. For synthetic compounds, accumulation in organisms generally depends on equilibrium between fat (in the organisms) and water solubility. Since most ketonic solvents are fairly water soluble, it appears unlikely that they will bioaccumulate in significant quantities in food chain organisms. Furthermore, methyl ketones are known to be rapidly attacked by microorganisms; and, therefore, they are not likely to be around to be taken up by the organisms.

In many instances, octanol-water partition coefficients have provided useful information regarding bioconcentration potential of chemicals. Neely et al. (1974) have reported a linear relationship between octanol-water partition coefficient and bioconcentration of chemicals in trout muscle. Using the equation of the straight-line of best fit, derived by Neely and coworkers, we have calculated the bioconcentration factor for those ketones for which octanol-water partition coefficient is available from the literature (Leo et al., 1971). The calculated bioconcentration potential of ketones is shown in Table 53. Since the partition coefficient for the ketones fall outside the range of the partition coefficients represented in the straight line of best fit, less confidence must be placed on these predictions. From the calculated values, it appears that ketones in general do not have high bioconcentration potentials. Of some concern may be the long chain methyl ketones, such as 2-hexanone, or alicyclic ketones, such as acetophenone. However, since these as well as other ketones will be susceptible to metabolism and excretion from the organism (unlike the compounds studied by Neely et al., 1974), the actual bioconcentration factor for the ketones may be lower than calculated from the method of Neely et al. (1974).

4. Biomagnification

Biomagnification indicates concentration of a compound through the consumption of lower organisms by higher food chain organisms with a net increase in tissue concentration (Isensee et al., 1973). No experimental data

Table 53. Bioconcentration Potential of Ketones in Fish (Calculated according to the Regression equation of Neely *et al.*, 1974)

Ketone	Log Octanol-Water Partition Coefficient 25°C*	Calculated Bioconcentration Factor
2-Butanone	0.26 - 0.29	1.84 - 1.91
2-Hexanone	1.38	7.447
Cyclohexanone	0.81	3.65
1-Hexen-5-one	1.02	4.753
Acetophenone	1.58	5.57

* Data obtained from Leo *et al.*, 1971

regarding biomagnification potential of ketones is available in the literature.

To some extent, the water solubility of ketones could be helpful in providing an approximate idea of their biomagnification potential. Metcalf and Lu (1973) have reported a relationship between water solubility and ecological magnification of 16 organic compounds which the authors evaluated in their model aquatic ecosystem. They obtained a regression equation for the line fitted by the method of least square. This relationship has been used here to predict the biomagnification potential of ketones from their water solubility. The results shown in Table 54 indicate that hardly any biomagnification of ketones in fish should be expected. Certain branched ketones and higher chain length ketones may be of some concern because of their relatively low water solubility and, hence, somewhat greater predicted ecological magnification potential (range between 6-8). In general, however, it is unlikely that ketones will bimagnify to a significant extent in the food chain organisms.

Table 54. Calculated Ecological Magnification of Ketones in Metcalf's Model Aquatic Ecosystem (see Metcalf and Lu, 1973)

Ketone	Log Water Solubility, ppb at 20°C	Calculated Ecological Magnification (fish) $\left(\frac{\text{concn. in fish}}{\text{concn. in water}}\right)$
Diethyl ketone	7.531	0.0
Diisopropyl ketone	8.22	0.0
Diisobutyl ketone	5.699	8.79
Methyl ethyl ketone	8.428	0.0
Methyl *n*-propyl ketone	7.633	0.0
Methyl *n*-butyl ketone	7.214	0.0
Methyl isobutyl ketone	7.278	0.0
Methyl *n*-amyl ketone	7.161	>1
Methyl isoamyl ketone	6.732	1.98
Methyl *n*-hexyl ketone	5.954	6.08
Ethyl *n*-butyl ketone	7.633	0.0
Ethyl *n*-amyl ketone	7.415	0.0
Mesityl oxide	7.447	0.0
Diacetone alcohol	—	0.0
Acetonylacetone	7.491	0.0
Cyclohexanone	7.398	0.0
Methylcyclohexanone		
Isophorone	7.07918	>1
Acetophenone	6.74	1.95

Method of Calculation:

The regression equation for the straight line plotted from the relationship between water solubility and ecological magnification in model aquatic ecosystem (Metcalf and Lu, 1973) is:

$$y = 7.205 - 1.595\,x$$

where y = log water solubility

x = log ecological magnification (fish)

B. Biology

1. Absorption

Previous reviews (Browning, 1965; Rowe and Wolf, 1963) have used the ability of certain ketones to cause systemic toxic effects as an indicator of absorption by various routes of administration. While this approach is probably valid for the ketonic solvents, it is not particularly illuminating because there is no way to distinguish between toxic potency and the rate of absorption. As detailed in later sections, almost all of the ketones can be lethal on oral, dermal, and inhalation exposures; thus, absorption, by these routes, may be assumed.

Little direct quantitative information is available on the absorption of ketonic solvents. Only Haggard and coworkers (1945) determined ketone blood levels. This work, however, involved a series of intraperitoneal injections to rats in an attempt to determine comparative toxicities of three amyl ketones. While offering useful data on ketone elimination (discussed in the appropriate sections below),no attempt was made to study absorption kinetics. In one instance in which a rat was injected with methyl isopropyl ketone (1 g/Kg), the first measurement of ketone blood levels taken one hour after dosing was about 83 mg ketone/100 ml of blood and rapidly declined thereafter (see Figure 34, p. 181). This pattern is indicative of relatively rapid absorption from the injection site.

The dermal absorption of methyl ethyl ketone on normal and hydrated skin surfaces using ketone in expired air as an index of absorption has been examined by Wurster and Munies (1965). Using human subjects, considerable variation was found between individuals in both the steady-state concentration of methyl ethyl ketone in expired air (2.54 - 13.00 μg/ℓ) and in the time required to reach the steady-state level (9-42 minutes). No correlation was found between these two values. As indicated in Figure 29, hydration of the stratum corneum caused a marked increase in both the peak and steady-state concentrations of methyl ethyl ketone in expired air. The decline in methyl ethyl ketone concentration from the peak value in hydrated skin is probably due to dehydration of the skin by the ketone. However, the higher steady-state value for hydrated skin suggests that the dehydration effect is only partial and that the water level in the hydrated skin remains above normal at least for the three hour experimental period (Wurster and Munies, 1965). Other ketones were not tested.

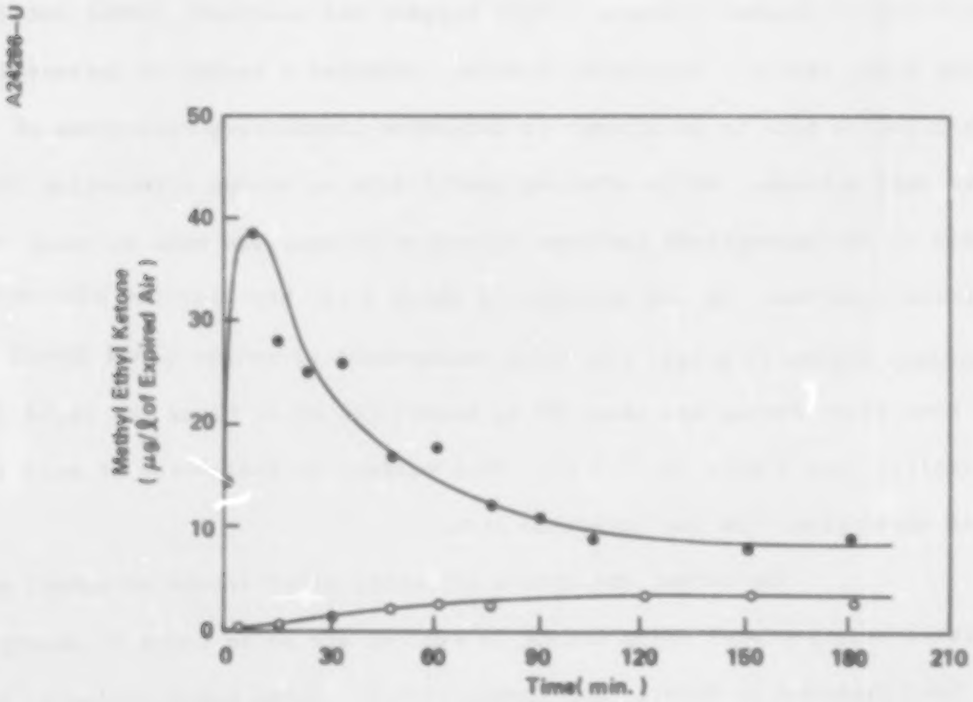


Figure 29. Expired air data showing the influence of moisture on the percutaneous absorption of methyl ethyl ketone. KEY: O, normal skin; ●, hydrated skin. (Wurster and Munies, 1965)

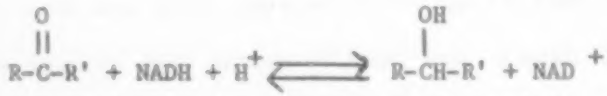
The level of glucuronic acid in plasma has been suggested as a means of following the absorption of cyclohexanone after oral administration to rabbits (Deichmann and Dierker, 1946). As will be discussed in a later section (see p. 175), glucuronide conjugation is a common route in the elimination of many ketones and an increase in glucuronic acid levels - after acid hydrolysis of the conjugate - can be used as an index of ketone exposure (e.g., Treon et al., 1943a or b). However, the results of Deichmann and Dierker (1946) indicate that this method may not be quantitatively reliable. At a dose of 760 mg/kg, maximum absorption occurred after two hours with a peak plasma glucuronide level of 15 mg/100 ml. At double this dose, peak absorption apparently occurred after seven hours with a peak plasma glucuronide level of 120 mg/ml. At a dose of 2840 mg/kg which was lethal in twenty-six hours, however, plasma levels peaked at only 43 mg/100 ml between three and five hours. In that urine glucuronide levels continued to remain high throughout the twenty-four hour observation period thus indicating that extensive absorption did occur, the low plasma glucuronide levels found with the high dose cast doubt on the suitability of this method for determining quantitative levels of ketone absorption.

2. Metabolism

a. Reduction Reactions

A variety of in vivo and in vitro investigations indicate that ketone reduction to the corresponding secondary alcohol may be a major route in ketone metabolism especially for the aliphatic and alicyclic ketonic solvents. Thus far, only three enzymes have been identified which catalyze this reaction (alcohol dehydrogenase, aromatic aldehyde-ketone reductase, and α,β-unsaturated ketone reductase), although additional enzymes may well be involved.

Alcohol dehydrogenase, which is well known for its role in the conversion of acetaldehyde to ethanol, has been shown to catalyze the reduction of certain ketones to the corresponding alcohols. The reaction, which is reversible and requires nicotinamide adenine dinucleotide ($NADH/NAD^+$), may be written as:



$$R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' + NADH + H^+ \rightleftharpoons R\text{-}\overset{OH}{\overset{|}{C}}H\text{-}R' + NAD^+$$

Winer (1958), using NADH levels to assay enzymatic activity, found that a variety of aldehydes and alcohols would serve as substrates for horse liver dehydrogenase. In addition, cyclohexanone but not methyl ethyl ketone or acetone was reduced. Under equivalent incubation conditions, the initial rate of cyclohexanone reduction was only one-sixth that of acetaldehyde. In the reverse reaction, however, the initial oxidation rate of cyclohexanol was equal to ethanol while an unspecified methylcyclohexanol was oxidized only 80% as rapidly as ethanol. The Km[*] for cyclohexanone was found to be 1.9×10^{-3}M (as opposed to 2.1×10^{-4}M for acetaldehyde) and 1.3×10^{-3}M for cyclohexanol (compared to 5.3×10^{-4}M for ethanol).

---

[*] The substrate concentration which gives a reaction velocity equal to one-half the maximum velocity.

The more detailed results of Merritt and Tomkins (1959) indicate that horse liver alcohol dehydrogenase is able to reduce certain alicyclic ketones but that the enzyme is quite sensitive to ring modification (see Table 55).

Table 55. Substrate Specificity of Horse Liver Alcohol Dehydrogenase (modified from Merritt and Tomkins, 1959)

Ketones	µ Moles Substrate Metabolized/E_{280}/minute	Corresponding Alcohol*	µ Moles Substrate Metabolized/E_{280}/minute
Acetaldehyde	68.2	Ethanol	9.74
Acetone	0.0	*sec*-Propanol	0.0
Methyl ethyl ketone	0.0	*sec*-Butanol	3.49
Cyclohexanone	8.52	Cyclohexanol	13.4
2-Methylcyclohexanone	3.86	2-Methylcyclohexanol	1.19
3-Methylcyclohexanone	3.05	3-Methylcyclohexanol	2.1
4-Methylcyclohexanone	6.84	4-Methylcyclohexanol	13.1
Cyclopentanone	0.0	Cyclopentanol	0.0
Cycloheptanone	3.52	Cycloheptanol	6.54

* Ketones and aldehydes tested at concentrations of 1.0×10^{-3}M, NADH 1.0×10^{-4}M, phosphate buffer, pH 7.2, 1.0×10^{-3}M.
Alcohols tested at concentrations of 1.0×10^{-3}M, NADH 1.0×10^{-4}M, NaOH-glycine buffer, pH 9.5, 1.0×10^{-3}M.

As in the study by Winer (1958), the oxidation of cyclohexanol proceeds at about the same rate as ethanol oxidation, while the reverse reaction - the reduction of cyclohexanone - is only one-eighth as rapid as that of acetaldehyde. In studying the kinetics of the cyclohexanone reaction, Merritt and Tomkins (1959) calculated a Km for cyclohexanol of 1.6×10^{-3}M - very close to that noted by Winer (1958), 1.3×10^{-3}M. For cyclohexanone reduction, however, Merritt and Tomkins (1959) found that the Km was dependent on cyclohexanone concentration showing negative cooperativity. At concentrations below 10^{-3}M the Km was 5.0×10^{-4}M but increased to 7.6×10^{-3}M at higher concentrations.

Methylation of the cyclohexanone ring causes a marked drop in reactivity. Elliott and coworkers (1969) found that the rates of oxidation and Km values varied markedly with both the position of the methyl group in the ring and the steric configuration of the methyl group (see Table 56).

Table 56. Michaelis Constant and Relative Rates of Reduction of Ketones (Elliott *et al.*, 1969)

	Km (molar)¶	Relative Ratesξ
(±)-2-Methylcyclohexanone	1.79×10^{-2}	1.1
(+)-2-Methylcyclohexanone	1.03×10^{-2}	3.6
(-)-2-Methylcyclohexanone	2.12×10^{-2}	0.4
(±)-3-Methylcyclohexanone	1.44×10^{-3}	57.6
(+)-3-Methylcyclohexanone	1.19×10^{-2}	1.1
(-)-3-Methylcyclohexanone	1.48×10^{-3}	68.1
4-Methylcyclohexanone	1.88×10^{-3}	40.3
Cyclohexanone	2.3×10^{-3}	100.0

¶ Km values were obtained from Lineweaver and Burke plots.

ξ Oxidation rates of ketones were compared with cyclohexanone at the same concentration

Although the results of Elliott and coworkers (1969) confirm the decreased reactivity of methylcyclohexanone and the stereospecific nature of the decrease, no concentration effect on cyclohexanone Km was noted.

The relative specificity for ring size is also apparent from Table 55. An increase in one carbon (cycloheptanone) reduces activity by about 50% and a decrease in one carbon (cyclopentanone) abolishes activity. The inability of acetone or methyl ethyl ketone to act as substrates for horse liver alcohol dehydrogenase indicates that a ring configuration may be necessary for ketone reduction. The moderate activity of sec-butanol does, of course, indicate that some alcohols analogous to the acyclic ketones may bind to the enzyme, but the inability of acetone to inhibit cyclohexanone reduction [detailed data not given by Merritt and Tomkins (1959)] suggests that the binding site for the cyclic compounds may be different from that of the acyclics.

The thermodynamics of cyclohexanone reduction by horse liver alcohol dehydrogenase approximates that of acetaldehyde reduction. The K_{eq} (aldehyde or ketone + NADH + H^+/alcohol + NAD^+) for acetaldehyde reduction is 8.6×10^{-12} giving an oxidation-reduction potential, E_o', of -0.280 volt; cyclohexanone reduction has an average K_{eq} of 5.5×10^{-9} with a E_o' of -0.200 volt (Merritt and Tomkins, 1959). While cyclohexanone reduction is somewhat less thermodynamically favorable than that of acetaldehyde, the similar E_o' values do indicate that horse liver alcohol dehydrogenase could play a significant role in the in vivo reduction of cyclohexanone and perhaps other related alicyclic ketones. Yeast alcohol dehydrogenase, however, does not catalyze this reduction for any of the above alicyclic ketones or the oxidation of the corresponding alcohols (Merritt and Tomkins, 1959; Winer, 1958).

An enzyme which will catalyze the reduction of certain aliphatic, alicyclic ketones and at least one acyclic aliphatic ketone has been partially purified from rabbit kidney cortex tissue (Culp and McMahon, 1968). The enzyme, referred to as aromatic A-K reductase, was also found in the kidney cortex of rats and hogs as well as in rabbit liver but not in heart, lung, or smooth muscle tissue. Like alcohol dehydrogenase, aromatic A-K reductase is associated with the cytosol. However, unlike alcohol reductase, the reaction is irreversible, requires NADPH rather than NADH, and shows different substrate specificity (see Table 57).

Table 57. Substrate Specificity of Aromatic A-K Reductase
(Modified from Culp and McMahon, 1968)

Substrate*	NADPH oxidized (µ Moles/min/mg protein)
Acetaldehyde	0**
Acetone	0
Diethyl ketone	24
Cyclopentanone	3
Cyclohexanone	452
# Acetophenone	42
p-Chloroacetophenone	280
p-Nitroacetophenone	635
Benzaldehyde	433
# p-Methoxybenzaldehyde	284
# p-Chlorobenzaldehyde	1283
# p-Nitrobenzaldehyde	1277

* Substrates tested at concentrations of 1 x 10^{-3} M, NADPH 1.6 x 10^{-4} M, sodium phosphate buffer 0.1 M and enzyme (0.05 to 5.0 mg protein/ 3 mℓ), at pH 7.0 and temperature of 25°C. Reaction assayed or NADPH oxidation determined as Δ O.D./t at 340 nm.

** Also no activity when NADH was substituted for NADPH

# Corresponding alcohols used to test for reversibility of reaction using both NAD^+ and $NADP^+$

As indicated in Table 57, the apparent irreversibility of the reduction is based on tests with the alcohol analogues of acetophenone and three substituted benzaldehydes. These tests were conducted at pH 10 using either $NADP^+$ or NAD^+. For the aldehyde analogues, semicarbazide was added to the reaction mixture to bind any aldehyde formed, thus facilitating oxidation. No aldehyde oxidation was noted.

That the enzyme is not alcohol dehydrogenase is apparent in the failure of acetaldehyde to serve as a substrate with either NADPH or NADH. The reduction of cyclopentanone, acetophenone, and diethyl ketone in addition to cyclohexanone suggests that aromatic A-K reductase could be involved in the metabolism of a variety of ketonic solvents resistant to degradation by alcohol dehydrogenase. Further studies on the substrate specificity of aromatic A-K reductase, however, have not been encountered, although this may have been the enzyme involved in the reduction of acetophenone noted by Maylin and Anders (1969) in rat liver post-microsomal supernatant.

Another NADPH-linked ketone reductase has been purified from the cytosol fraction of dog erythrocytes and human liver. This enzyme, however, is specific for α,β-unsaturated ketones. Of the ketonic solvents under review, the enzyme has been shown to reduce 3-buten-2-one (Km of 7.8×10^{-4}M in erythrocyte enzyme and 2.8×10^{-4}M in liver enzyme), but not methyl ethyl ketone or 2-cyclohexen-1-one. NADPH consumption and substrate reduction showed an approximate 1:1 ratio suggesting that either the keto group or the carbon-carbon double bond, but not both, was reduced (Frazer *et al.*, 1967).

Thus, three enzymes have been specifically identified in ketone reduction - alcohol dehydrogenase, aromatic A-K reductase, and α,β-unsaturated ketone reductase - all associated with the cytosol. This is consistent with the results of Leibman (1971), who examined the in vitro metabolism of various ketones in complete cytosol and microsomal fractions, rather than partially purified enzyme preparations, and found that ketone reduction occurred almost exclusively in the cytosol. Similar to the tissue distribution of aromatic A-K reductase noted by Culp and McMahon (1968), Leibman (1971) found that acetophenone reduction occurred primarily in the liver and kidney, to a lesser extent in the heart and lung, and not at all in the brain cytosol of rabbits (see Table 58).

Table 58: Acetophenone Reduction in Various Rabbit Tissue Cytosols (Leibman, 1971)

Organ	Initial rate of NADPH oxidation (nmol/min/100 mg tissue)
Liver	138
Kidney	96
Heart	30
Lung	30
Brain	0

However, Leibman (1971) also found that both NADPH and NADH could serve as reducing agents for acetone, methyl ethyl ketone, or acetophenone (see Table 59).

Table 59. **Oxidation of Pyridine Nucleotides in Rabbit Liver Cytosol in the Presence of Ketones** (Leibman, 1971)

Ketone	Concentration of Ketone	Nucleotide	Initial Rate of Oxidation (nmol/min/100 mg[#] liver)
Acetone	1 M	NADPH	283
		NADH	296
Methyl ethyl ketone	50 mM	NADPH	157
		NADH	173
Acetophenone	8 mM	NADPH	278
		NADH	25
None	–	NADPH	8
		NADH	<5

These results suggest at least two mechanisms for ketone reduction: one dependent on NADPH which reduces both aromatic and aliphatic ketones and the other dependent on NADH which reduces aliphatics with equal facility but is less able to reduce aromatic ketones. These NADPH and NADP dependent reductions may reflect the activity of a number of different cytosol enzymes rather than just the NADH-dependent alcohol dehydrogenase and NADPH-dependent aromatic A-K reductase discussed above. This seems probable in that neither of these enzymes could catalyze the reduction of acetone, and alcohol dehydrogenase did not reduce methyl ethyl ketone (Merritt and Tomkins, 1959 - see Table 55; Culp and McMahon, 1968 - see Table 57). Nevertheless, it is also possible that the higher concentrations of acetone and methyl ethyl ketone used by

Leibman (1971) facilitated ketone reduction by alcohol dehydrogenase, aromatic A-K reductase or other enzymes in the cytosol. However, at least one enzyme in addition to alcohol dehydrogenase and aromatic A-K reductase is implicated by the reversibility of NADPH- and NADH-mediated acetophenone reduction (see Table 60).

Table 60. Reversibility of Acetophenone Reduction in Rabbit Liver Cytosol (Leibman, 1971)

Substrate (8×10^{-3}M)	Nucleotide (2×10^{-4}M)	Initial rate of oxidation or reduction (nmol/min/100 mg liver)
Acetophenone	NADPH	320
	NADH	128
1-Phenylethanol	NADP	320
	NAD	152

In this instance, the substrate and nucleotide concentrations are similar to those used by Culp and McMahon (1968) [1×10^{-3}M for substrate and 1.6×10^{-4}M for nucleotide] who found that aromatic A-K reductase could not catalyze the oxidation of 1-phenylethanol to acetophenone.

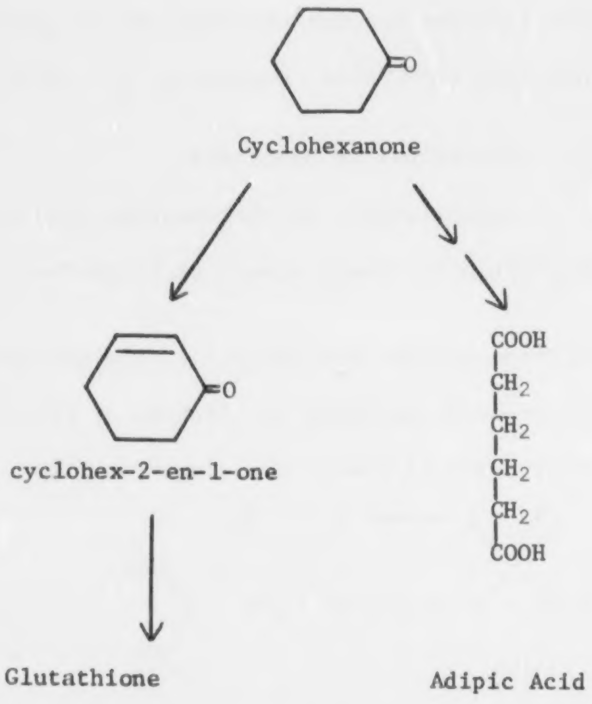
The reversibility of ketone reduction noted by Leibman (1971) for acetophenone and by Merritt and Tomkins (1959) for many horse liver alcohol dehydrogenase reactions is also indicated by in vivo studies of secondary alcohol metabolism. Haggard and coworkers (1945) have noted the rapid and extensive conversion of three amyl alcohols (pentan-3-ol, pentan-2-ol, and 3-methyl butan-2-ol) to the corresponding ketones (diethyl, methyl n-propyl, and methyl isopropyl, respectively) after intraperitoneal injection of rats with these alcohols. In a similar experiment administering a variety of secondary alcohols to rabbits by intubation, Kamil and coworkers (1953) found that the following alcohols were converted to ketones to some extent: DL-butan-2-ol to methyl ethyl ketone, hexan-2-ol to methyl ketone (presumably methyl _n_-butyl ketone), and 4-methylpentan-2-ol to methyl isobutyl ketone. However, contrary to the results of Haggard and coworkers (1945), pentan-2-ol and pentan-3-ol were not oxidized. Whether this is attributable to the differences in route of administration or species exposed cannot be determined from the available data.

As evidenced by the information thus far presented, a variety of ketones are converted to the corresponding secondary alcohols prior to elimination. The various reductions are catalyzed by one of at least three enzymes which are associated with the cytosol, occur primarily in the liver and kidneys, and require NADPH or NADH. While some of the individual reactions may be irreversible in pure enzyme preparation, ketone/alcohol conversion seems to be reversible _in vivo_. Most information available on the rate of such reductions _in vitro_ (see Table 55, 57, and 59) suggests that compounds containing aromatic or cyclohexyl rings are much more readily reduced than low molecular weight acyclic aliphatic ketones. This is consistent with _in vivo_ studies on various mammals indicating that the following aliphatic and cyclohexyl ketones are reduced to corresponding alcohols in appreciable amounts prior to conjugation: acetophenone, 47% (Smith _et al._, 1954a); benzophenone, 50% (Robinson, 1958); cyclohexanone, 51-80% (Elliott _et al._, 1959); 2-, 3-, and 4-methylcyclohexanone, 72-80% (Elliott _et al._, 1965); and 2-, 3-, and 4-_tert_-butylcyclohexanone, 76.5-80% (Cheo _et al._, 1967) [see Table 64, p. 185 for details of these studies]. However, it should also be noted that the metabolism of higher acyclic aliphatic ketones has received relatively little attention. Kamil and associates (1953) have noted that 45.2% of methyl n-amyl ketone is apparently reduced to heptan-2-ol after oral administration to rabbits. Thus, the enzymatic apparatus may well exist for the reduction of at least some aliphatic ketones. The predominance of reduction in the metabolism of a particular ketone seems related to the degree of glucuronide or sulfate conjugation with subsequent urinary elimination. Quantitative aspects of this process are discussed in the section on elimination (see p. 184) while the general pattern of ketone conjugation is discussed in part (d) of this section (see p. 175).

b. Oxidation

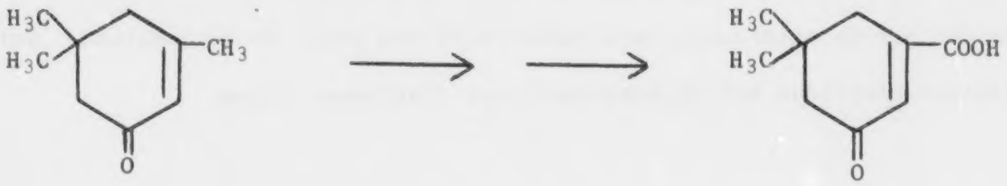
Perhaps the most important ketone oxidation reaction is the conversion of methyl n-butyl ketone to 2,5-hexanedione. As discussed in Section III-D-3 (p. 266), this dione may be the neurotoxic agent associated with the neuropathogenic properties of both methyl n-butyl ketone and n-hexane. This conversion seems to proceed by hydroxylation of the γ carbon forming 5-hydroxy-2-hexanone. This, in turn, is either reduced to 2,5-hexanediol or further oxidized to 2,5-hexanedione. This latter metabolite appears to predominate in the serum and could be reduced to 5-hydroxy-2-hexanone, but is not significantly converted to the diol. Both methyl isobutyl ketone and methyl ethyl ketone undergo corresponding oxidative/reductive metabolic conversion (DiVincenzo et al., 1976). These findings are consistent with those of Abdel-Rahman and coworkers (1975) showing that rats, guinea pigs, and rabbits exposed to methyl n-butyl ketone vapor excrete 2-hexanol and 2,5-hexanediol in the urine principally as O-glucuronides.

Alicyclic ketone oxidation has been long recognized. Adipic acid, excreted in the urine, has been cited as a minor metabolite of cyclohexanone after intraperitoneal injection of both mice (Filippi, 1914) and guinea pigs (Frey, 1939). In addition, Boyland and Chasseau (1970) have found that cyclohexanone, injected intraperitoneally into rats, lowers liver glutathione levels. Since cyclohexanone does not have an activated double bond and does not undergo glutathione conjugation _in vitro_, these investigators have speculated that cyclohexanone may be oxidized to cyclohex-2-en-1-one prior to conjugation. Both oxidation reactions for cyclohexanone are diagrammed below.


Cyclohexanone
cyclohex-2-en-1-one
COOH
CH2
CH2
CH2
CH2
COOH
Glutathione
Adipic Acid

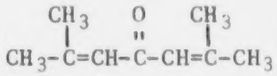
The cyclohex-2-en-1-one reaction is apparently a simple dehydrogenation. Adipic acid formation, however, would require at least one intermediate, the identity of which has neither been determined nor proposed.

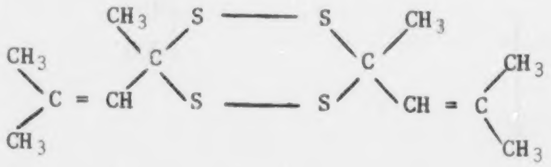
Isophorone also appears to undergo oxidation of the 3-methyl group after oral administration of 1 g/kg to rabbits. This reaction, shown below, precedes glucuronide conjugation and urinary elimination.



The pathway of this reaction and the structure of the glucuronide conjugate formed have not yet been identified (Truhaut _et al_., 1970).

c. **Miscellaneous Reactions**

Lewin (1907), in subcutaneous injections of rabbits with mesityl oxide and phorone [a linear isomer of isophorone,  $CH_3-\overset{CH_3}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-CH=\overset{CH_3}{\overset{|}{C}}-CH_3$], has proposed that these ketones are converted to disulfide compounds. The proposed metabolite of mesityl oxide involves the linking of two such sulfur substituted molecules of mesityl oxide by disulfide bridges to give:



Additional studies supporting the formation of this proposed metabolite have not been encountered.

d. Conjugation Reactions

Many of the ketonic solvents have been shown to undergo conjugation with glucuronic acid, sulfate, or glutathione prior to renal excretion. Glucuronic acid conjugation may proceed via either ketone reduction to the corresponding secondary alcohol or ketone oxidation to a carboxylic acid derivative. The formation of sulfuric acid esters (ethereal sulfates) by sulfate conjugation probably occurs exclusively through secondary alcohol formation. Glutathione conjugation, with subsequent mercapturic acid formation, seems restricted to the alicyclic ketones and does not involve alcohol or carboxylic acid formation. This general outline of ketone conjugation reactions is summarized in Figure 30.

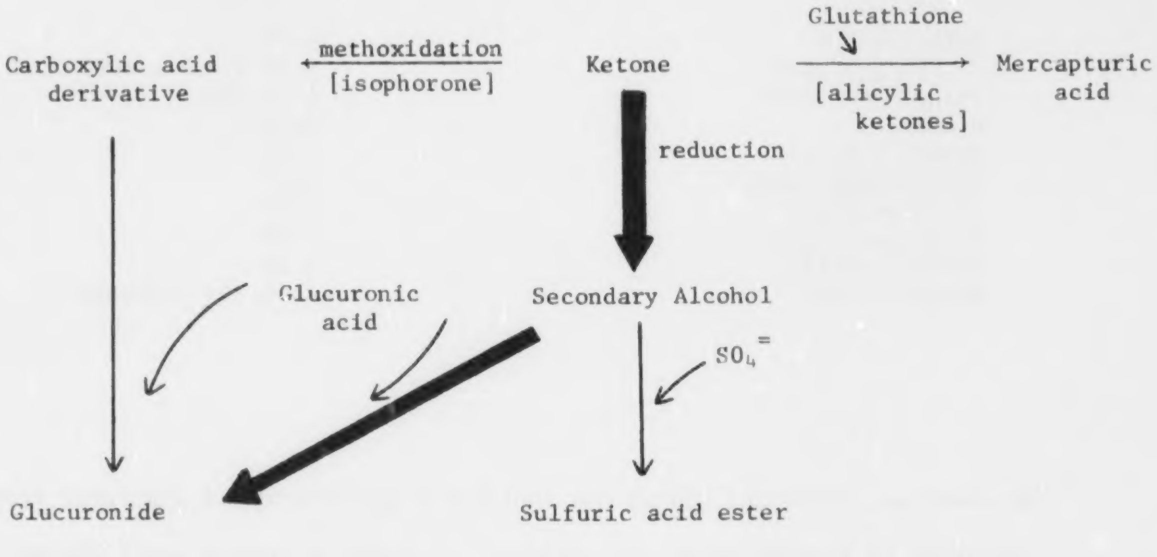

Glutathione
Carboxylic acid derivative
methoxidation
[isophorone]
Ketone
[alicylic ketones]
Mercapturic acid
reduction
Glucuronic acid
Secondary Alcohol
$SO_4^=$
Glucuronide
Sulfuric acid ester

Figure 30. Overview of Ketone Conjugation Reactions

➡ major route

Of the conjugation routes given in Figure 30, glucuronic acid formation is by far the most common. Although conjugation does not seem to be a quantitatively significant pathway in the elimination of most acyclic aliphatic ketones (see Section III-B-3, Elimination, p. 184), Neubauer (1901) as indicated in Table 61, has demonstrated that many of these ketones cause an increase in urinary glucuronic acid levels after oral administration to rabbits.

Table 61. Ketones Causing Increases in Glucuronic Acid Urinary Excretion After Oral Administration to Rabbits (Neubauer, 1901)

Ketone	Dose (g/kg)
Methyl ethyl	0.96
Methyl *n*-propyl	1.40 (in 2 doses)
Methyl isopropyl	1.37 (in 2 doses)
Diethyl	1.03
Methyl *n*-butyl	1.06
Methyl *tert*-butyl	1.01
Ethyl *n*-propyl	1.02
Ethyl isopropyl	0.85
Methyl *n*-hexyl	1.35
Mesityl oxide	1.33 (in 3 doses)

In addition, Saneyoshi (1911) has isolated a glucuronide of 2-butanol from the urine of rabbits which had received 2-3 grams of methyl ethyl ketone (2-butanone) in the diet. However, the only acyclic aliphatic ketone which has been shown to undergo extensive glucuronide conjugation is methyl *n*-hexyl ketone (42% of dose) after oral administration to rabbits (Kamil *et al*., 1953; see Table 64, p. 185).

All alicyclic ketones, however, are conjugated to a marked degree, primarily as glucuronides. Indirect evidence of cyclohexanone and methylcyclohexanone conjugation is presented by Deichmann and Thomas (1943) who noted that oral administration of these ketones to rabbits resulted in greatly increased glucuronic acid levels and slightly depressed inorganic sulfate levels in the urine. Treon and coworkers (1943 a & b) have noted similar results after both oral and inhalation exposures to these ketones. The increased glucuronic acid levels in urine parallel similar increases in plasma and serum glucuronic acid after oral administration of cyclohexanone to rats (Deichmann and Dierker, 1946).

Since these early investigations, the conjugation products of the alicyclic ketones have been isolated and identified. Cyclohexanone is conjugated primarily as the glucuronide of cyclohexanol (Elliott _et_ _al_., 1959), although small amounts of the sulfuric acid ester and 2-hydroxycyclohexylmercapturic acid and its sulfate ester are also formed. Similar patterns are followed by both cyclopentanone and cycloheptanone (James and Waring, 1971). Methylcyclohexanones (Elliott _et_ _al_., 1965) and _tert_-butylcyclohexanones (Cheo _et_ _al_., 1967) are also conjugated as glucuronides and sulfuric acid esters of the corresponding alkyl cyclohexanols, but no indication of mercapturic acid formation was found. In that glutathione derivatives of the unsubstituted alicyclics occur in only trace amounts (James and Waring, 1971) and the analytical technique used by Elliott and coworkers (1965) and Cheo and coworkers (1967) has a recovery of ±5% (Stekol, 1936), small quantities of methylcyclohexylmercapturic acid may have gone undetected.

Aromatic ketones undergo similar conjugation reactions. Acetophenone is conjugated primarily as methyl phenyl carbaryl glucuronide, although conjugation with glycine to form _n_-benzoylylione (hippuric acid) via benzoic acid also occurs (Smith _et al._, 1954a; Thierfelder and Klenk, 1924b). In addition, a small amount of acetophenone is conjugated with sulfate (Smith _et al._, 1954a). Mercapturic acid formation, however, has not been noted. Benzophenone undergoes glucuronic acid, but not sulfuric acid, conjugation as benzhydrol. This is in contrast to _p_-hydroxybenzophenone which is directly conjugated with glucuronic acid at the free hydroxyl group (Robinson, 1958).

Since these conjugation reactions are closely associated with ketone elimination, the quantitative aspects and experimental details of the above studies are discussed in the following section (p. 184).

3. Excretion/Elimination

a. Elimination as Free Ketone

Although most of the ketones examined seem able to undergo reduction reaction, many acyclic ketones seem to be eliminated unchanged in expired air and urine. In fact, many of the ketonic solvents are normal constituents of human urine. This was first suggested by Tsao and Pfeiffer (1957) who found traces of methyl ethyl ketone in urine of healthy adults. Zlatkis and coworkers (1973) subsequently found a variety of acyclic ketones in normal urine along with a few additional acyclic ketones and cyclohexanone in the urine of individuals with diabetes mellitus (see Table 62). Three of these ketones -- methyl ethyl, methyl *n*-propyl, and di-*n*-propyl -- are considered key components in the profile of normal urine (Zlatkis *et al.*, 1973).

Table 62. Ketone Components of Normal Human Urine and the Urine of Individuals with *Diabetes Mellitus* (After Zlatkis *et al.*, 1973)

Ketone	Present in Normal Human Urine	Urine of Individuals with *Diabetes Mellitus*
Solvents		
Acetone	+	+
Methyl ethyl Ketone	+	+
Methyl *n*-propyl Ketone	+	+
Methyl isobutyl Ketone	+	+
Methyl *n*-amyl Ketone	+	+
Methyl *n*-heptyl Ketone	+	+
Ethyl *n*-propyl Ketone	+	+
Ethyl *n*-butyl Ketone	-	+
Dipropyl Ketone	+	+
Ethyl *n*-amyl Ketone	+	+
Mesityl oxide (tentatively)	+	-
Cyclohexanone	-	+
Other Ketones		
3-methyl-2-butanone	+	+
2,3-butanedione	+	+
3-methyl-2-pentanone	+	+
5-methyl-3-hexanone	+	-
3-penten-2-one	+	+
6-methyl-3-heptanone	+	+
3-methyl cyclopentanone	+	+
3-hydroxy-2-butanone	-	+

In acute exposures to the acyclic ketones, elimination of unchanged ketones in the expired air may also be a major route of elimination. This is, perhaps, to be expected, since many of these ketones have low boiling points and high vapor pressures (Williams, 1959).

In studying the rate of elimination of three amyl alcohols injected intraperitoneally into rats at doses of 1 g/kg, Haggard and coworkers (1945) found that most of the alcohol was rapidly converted to the corresponding ketone and subsequently eliminated as ketone in the expired air and, to a much lesser extent, in the urine (see Figures 31-33). In addition, approximately 100% of an intraperitoneal injection of methyl isopropyl ketone was eliminated within 25 hours in the expired air and urine (see Figure 34).

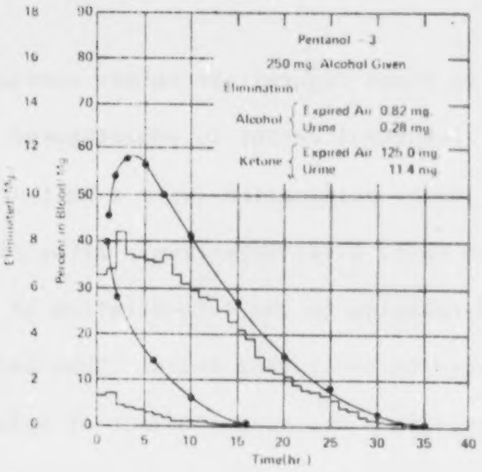


Figure 31. Concentrations of pentanol-3 and diethyl ketone in blood and loss by elimination in expired air and urine after administration of 1 g/kg. Lower curves, alcohol; higher curves, ketone.

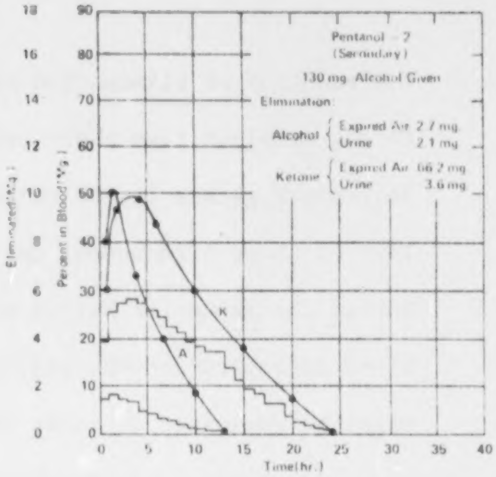


Figure 32. Concentrations of pentanol-2 and methyl n-propyl ketone in blood and loss by elimination in expired air and urine after administration of 1 g/kg of the alcohol. Curve A, alcohol; K, ketone.

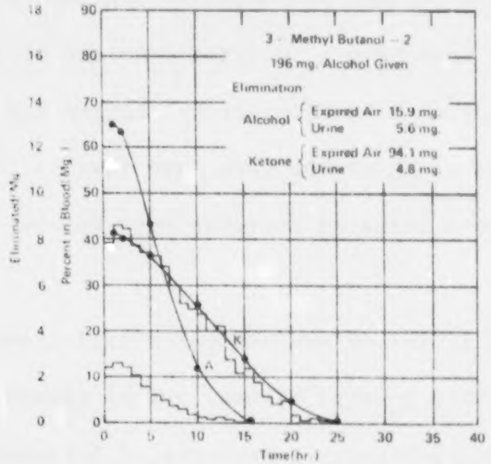


Figure 33. Concentrations of 3-methyl butanol-2 and methyl isopropyl ketone in blood and loss by elimination in expired air and urine after administration of 1 g/kg of the alcohol. Curve A, alcohol; K, ketone.

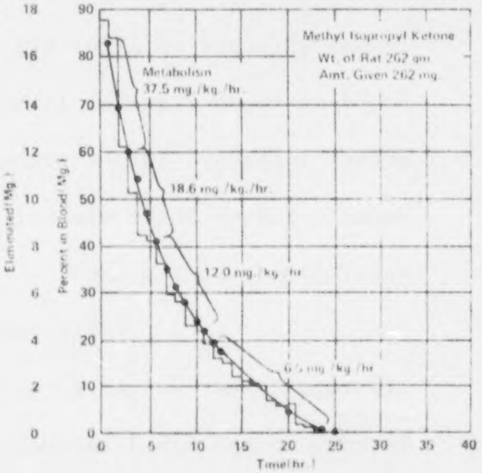


Figure 34. Rate of metabolism of methyl isopropyl ketone in the rat as determined from elimination in expired air and urine and disappearance from the blood.

Figures 31-34 from Haggard and coworkers, 1945.

The kinetics of elimination presented in these figures are rather complex. In the simplest case where only methyl isopropyl ketone is administered (Figure 34),ketone plasma levels reflect first order elimination (with a half-life of about 5.28 hours) up to fifteen hours after injection. After fifteen hours, the amount of ketone eliminated relative to the concentration in the blood increased and the half-life dropped to under four hours. This pattern might be explained in terms of the respiratory depressant effect of methyl isopropyl ketone. As the ketone blood level falls below about 12 mg per 100 ml blood at fifteen hours after injection, the respiratory rate may increase and thus result in a proportionately greater elimination of the ketone in expired air. However, since quantitative data on the effect of ketone blood levels and respiratory rate is not presented, the above explanation is speculative. Whatever the actual cause, similar patterns are presented in Figures 31-33 for ketone elimination after all alcohols have been eliminated from the blood. Based on these figures, it would appear that methyl _n_-propyl ketone and methyl isopropyl ketone are eliminated at about the same rate (half-life under 4 hours) while diethyl ketone is eliminated somewhat more slowly (half-life over 5 hours).

DiVincenzo _et al_. (1976) determined serum half-lives and clearance times in guinea pigs for methyl _n_-butyl ketone, methyl isobutyl ketone, methyl ethyl ketone, 2-hexanol, 5-hydroxy-2-hexanone, 2,5-hexanedione and 2,5-hexanediol. Clearance times after a single i.p. dose of 450 mg/kg dissolved in 25% corn oil were as follows: 2,5-hexanedione was almost three times as long as for MBK and MIBK and twice as long for 2,5-hexanediol and 5-hydroxy-2-hexanone. Clearance time for methyl ethyl ketone was twice as long as that for methyl n-butyl ketone.

Schwarz (1898) found that varying amounts of methyl ethyl ketone, methyl n-propyl ketone, and diethyl ketone were eliminated in the expired air of dogs in a twenty-four hour period after oral administration (see Table 63).

Table 63. Elimination of Ketones in the Expired Air of Dogs 24 Hours After Oral Administration (Schwarz, 1898)

Ketone	Expt. No.	Body Weight of Dogs in Grams	Mg Ketone per Dose	Mg Ketone per 1 kg Body Weight	Mg Ketone Eliminated	% of Ketone Eliminated in Expired Air
Methyl ethyl Ketone	1	4350	1723	396	522	30.3%
	2	3600	1216	338	402	33.1%
Methyl propyl Ketone	1	3300	1181	358	250	21.2%
	2	3950	1505	381	408	27.1%
Diethyl Ketone	1	3000	996	332	88	8.8%
	2	3170	346	109	-	-

- Translated from Schwarz, 1898, p. 190

The amount of diethyl ketone eliminated after 24 hours is less than would be expected from the results of Haggard and coworkers (1945). Again, insufficient data is presented to account for the apparent discrepancy which may or may not indicate quantitative species specific differences in routes of ketone elimination.

b. Elimination as Conjugation Products

The other major route of ketone elimination is conjugation with subsequent excretion of the conjugate in the urine. As mentioned previously, this is a major mode of elimination for the aromatic and alicyclic ketones and for at least one acyclic aliphatic ketone (methyl n-amyl ketone). The primary studies supporting this conclusion are summarized in Table 64. In addition, Truhaut and coworkers (1970) have reported that isophorone is eliminated in the urine as a glucuronide. Quantitative data on the extent of glucuronic conjugation, however, is not available.

It should be emphasized that none of the investigations summarized in Table 64 are balance studies -- i.e., no attempt is made to recover 100% of the dose, and to determine alternate routes of elimination or patterns of tissue distribution and storage. The recovery of over ninety percent of dose for both an unspecified mixture of methylcyclohexanones and for (±) 3-tert-butylcyclohexanone is fortuitous, indicating only that these ketones are eliminated almost exclusively as conjugates in the urine. The recovery of around 50% of the dose for most of the other ketones severely limits the utility of these studies in assessing total patterns of ketone elimination.

A comparison of Table 64 with Table 55 (p. 163) will show that in vitro studies on ketone reduction do not correlate with the observed in vivo conjugation of the alicyclic ketones. The order of alicyclic ketone reduction in vitro is cyclohexanone > methylcyclohexanones ≃ cycloheptanone >>> cyclopentanone. The order of ketone conjugation in vivo, however, appears to be methylcyclohexanones > cyclohexanone ≃ cycloheptanone > cyclopentanone.

Table 64. Ketone Conjugation and Renal Excretion in Rabbits

Ketone	Animal	Route of Administration	Dose	Duration of Test	% of Dose Eliminated - (range)				% of Dose Recovered	Reference
					Glucuronide	Sulphate Ester	Mercapturic Acid	Other		
Methyl *n*-amyl ketone	Chinchilla Rabbits (3) 3 kg each	Intubation	950 mg/kg	24 hrs	41%	0	n.d.	Small amount of unchanged ketone in urine	41%+	Kamil *et al.*, 1953
Cyclopentanone	Rabbits, female, Wistar strain, 200-250 g (3)	Intubation	193 mg/kg	24 hrs	47% (39-58)	2% (0-5)	trace	Sulfur-containing metabolite 25% (2.2-2.7)	51.5%+	James and Waring, 1971
Cyclohexanone	Rabbits, female, Wistar strain, 200-250 g (3)	Intubation	186 mg/kg	24 hrs	51-86%	n.d.	trace	Sulfur-containing metabolite 1.6% (1.5-1.6)	52.5-87.6%	James and Waring, 1971
	Rabbits, young (2)	Intubation	890 mg/kg	4 days	45-50%	+	n.d.		40-50%+	Treon *et al.*, 1943a
	Chinchilla Rabbits, Female (4)	Intubation	248 mg/kg	18 hrs	66% (51-86)	n.d.	n.d.	No free ketone in urine	51-86%	Elliott *et al.*, 1959
Methylcyclohexanone - Isomer not specified -	Rabbits, young (2)	Intubation	560 mg/kg	3 days	92%	+	n.d.		92%+	Treon *et al.*, 1943a
(±) 2-Methylcyclohexanone	Rabbits, young (2)	Intubation	516 mg/kg	24 hrs	72.3% (53.4-92.6)	0.9% (0.0-2.6)	0		73.2%	Elliott *et al.*, 1959
(±) 3-Methylcyclohexanone			572 mg/kg	24 hrs	73.6% (49.8-89.7)	2.2% (0.5-4.0)	0		75.8%	
4-methylcyclohexanone			607 mg/kg	24 hrs	80.3% (74.7-85.9)	1.1% (0.0-3.2)	0		81.4%	
(±) 2-*tert* butylcyclohexanone	Rabbits, female, 1-2 kg (3)	Intubation	645 mg/kg	24 hrs	76.5% (71-82)	"negligible"	0		76.5%	Choo *et al.*, 1967
(±) 3-*tert*-butylcyclohexanone			645 mg/kg	24 hrs	93.5%	"negligible"	0		93.5%	
4-*tert*-butylcyclohexanone			555 mg/kg	24 hrs	80.0% (74-87)	"negligible"	0		80%	
Cycloheptanone	Rabbits, female, Wistar strain, 200 g-250 g (3)	Intubation	190 mg/kg	24 hrs	60% (58-86)	14% (12-15)	trace	Sulfur-containing metabolite 1.0% (1.0)	75%	James and Waring, 1971
Acetophenone	Chinchilla Rabbits (3) 3 kg each	Intubation	450 mg/kg	24 hrs	47% (40-55)	3%	n.d.		50%	Smith *et al.*, 1954a
	Rabbits	Intraperitoneal injection	2 g per animal	n.s.	48.8%	n.d.	n.d.		48.8%	Thierfelder and Klenk, 1924a
Benzophenone	Rabbits (3)	Intubation	364 mg/kg	24 hrs	50% (46-61)	0	n.d.		50%	Robinson, 1958

n.s. = not specified

n.d. = not determined

The significant degree of cyclopentanone conjugation in vivo again suggests that additional enzymes are involved in ketone metabolism or that the activities of the enzymes studied in vitro were considerably altered during isolation.

Data on the rate of elimination of the ketones which undergo extensive conjugation are limited to measurements of glucuronic acid and inorganic sulfates (as percent of total sulfates) in twenty-four urine samples of rabbits receiving oral doses of cyclohexanone and methylcyclohexanone. This information is summarized in Table 65 . A rise in glucuronic acid and a decrease in the percent of inorganic sulfates indicate increased excretion of the ketones as glucuronides and sulfuric acid esters, respectively. (Deichmann and Thomas, 1943; Treon et al., 1943a). As Table 65 indicates, glucuronic acid and sulfate levels return to normal one to two days after ingestion of both ketones with methylcyclohexanone apparently eliminated somewhat more rapidly.

In a subsequent study, Deichmann and Dierker (1946) followed the glucuronic acid levels in hourly samples of plasma and urine of rabbits over a twenty-four hour period after the oral administration of cyclohexanone at 750 mg/kg, 1518 mg/kg, and 2840 mg/kg, using one rabbit at each dose level. At the lower dose, which approximates those of Table 65, both plasma and urine glucuronic acid levels peaked after two hours (15 mg glucuronic acid/100 ml plasma), dropped rapidly between two and four hours, and returned to normal after twenty-four hours. At the intermediate dose, plasma glucuronic acid peaked after seven hours to over ten times the concentration of the lower dose (1518 mg glucuronic acid/100 ml plasma)

Table 65. Excretion of Glucuronic Acids and Sulfates in 24 Hour Urine Samples of Rabbits Following Oral Administration of Cyclohexanone and Methylcyclohexanone*

Cyclohexanone			Methylcyclohexanone		
Days After Dose	% Inorganic Sulfates	Glucuronic acid(mg)	Days After Dose	% Inorganic Sulfates	Glucuronic acid(mg)
	[Dose]			[Dose]	
	890 mg/kg (1)			560 mg/kg (1)	
1	38.4	858	1	75.0	2,133
2	30.8	2,632	2	94.4	306
3	71.1	76	3	94.2	81
4	92.7	81			
	890 mg/kg (1)			522 mg/kg (2)	
1	58.3	2,133	1	80	944
2	62.5	1,090	2	90	160
3	90.1	78	3	85	-
4	89.2	49			
	947 mg/kg (2)				
1	60	1,246			
2	75	100			
3	80	30			

Normal Daily Excretion of Glucuronic Acid in Rabbits, 35.2 mg±24.8 [S.D.] (2)
Normal % Urinary Sulfates As Inorganic Sulfates, Approximately 85% (1)

* Is[illegible]s) not specified

(1) Tre[illegible], *et al.*, 1943a (2) Deichmann and Thomas, 1943

and then decreased gradually, returning to normal after twenty-four hours. Urinary glucuronides, however, remained elevated after twenty-four hours. This would suggest that cyclohexanone is eliminated relatively rapidly from the blood and deposited in the body, while urinary elimination takes place gradually over a more prolonged period. The animal receiving the highest dose died after twenty-six hours and eliminated about 50% less cyclohexanone/unit dose than the rabbit given the intermediate dose. This may indicate that acute cyclohexanone poisoning has an inhibitory effect on cyclohexanone elimination. However, because so few animals were used in this study, no firm conclusions are possible.

Although oral administration is the most commonly used method of exposure in metabolism studies of ketones, Treon and coworkers (1943b) have shown a direct relationship between the concentration of methylcyclohexanone in air and the degree of sulfate and glucuronide conjugation in rabbits (see Figure 35).

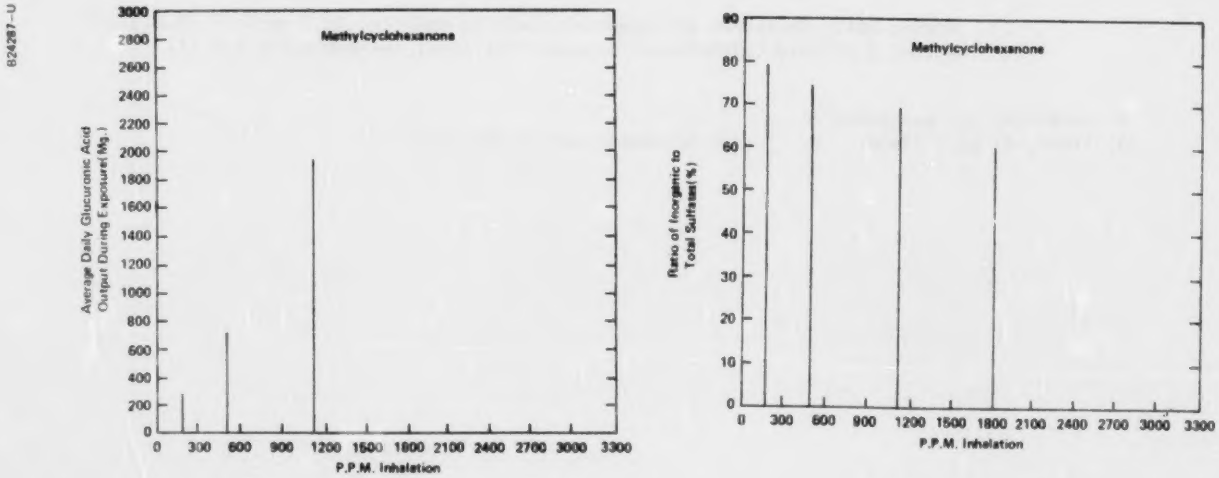


Figure 35. Influence of Methylcyclohexanone Inhalation on Glucuronic Acid (A) and Sulfate Elimination (B) in Rabbit Urine (Treon _et al._, 1943b)

A similar relationship for cyclohexanone exposures was not demonstrated. However, inhalation of cyclohexanone did have the general effect of increasing glucuronic acid and decreasing inorganic sulfate elimination in rabbit urine.

4. Transport, Distribution, and Storage

No direct information is available on any of these aspects of ketone biology. Of course, certain deductions can be made based on information presented above -- e.g., methyl ethyl ketone can be absorbed through the skin and transported to the lungs, presumably by the circulatory system, where the ketone is then eliminated in expired air.

As described previously (see Section I-A-2, Physical Properties, p. 4), all of the ketonic solvents under review are extremely soluble in organic solvents, but the water solubility of the acyclic aliphatic ketones decreases with increasing molecular weight. Nelson and Hoff (1968) have found that the partition coefficients (mineral oil vs. Na_2SO_4 saturated aqueous solution) increase going from acetone (0.345), to methyl ethyl ketone (3.21), to methyl n-butyl ketone (20.7). Mesityl oxide, which is very slightly soluble in water, but readily soluble in organic solvents, does seem to be stored in guinea pigs in that repeated inhalation exposures to subanesthetic concentrations leads to death from narcosis (Smyth et al., 1942). Jeppsson (1975) has recently evaluated the effect of lipophilicity on ketone toxicity and concluded that highly lipophilic compounds may be less toxic because they are preferentially sequestered in lipid components and do not reach receptor sites. Thus, lipid storage, for at least some water-insoluble ketones, does seem likely.

C. Human Toxicity

In an occupational environment, workers are most likely to be exposed to the ketonic solvents dermally or by inhalation. The ketone vapors enter the body through the mucous membranes of the nose, eyes, and respiratory tract. Skin contact with the solvent leads to ready absorption of some ketones due to their high lipid solubility. The volatility of these compounds has some influence on dermal absorption, with rapid evaporation limiting actual absorption. Voluntary ingestion of the ketones is uncommon.

The ketone vapors are generally found to be irritating to the eyes and nose at relatively low concentrations and, therefore, allow sufficient warning of exposure, thus limiting the danger of gross overexposure. However, for some of the solvents, these 'warning signs' and irritations do wear off to some extent, and limited tolerance to the vapors can be acquired during the work week; however, this tolerance is lost over the weekend and must be reacquired (Vernot et al., 1971; Elkins, 1959). Rowe and Wolf (1963) state that lower concentrations of the vapors may not cause discomfort, but can cause impairment of judgement and thereby create a secondary hazard. Such an effect has been noted by Nakaaki (1974), who found that methyl ethyl ketone altered estimates of time periods at vapor concentrations causing only minor eye and throat irritation. The solvent vapors are also known to produce headache, nausea with vomiting, dizziness, and drowsiness to some degree. At higher concentrations, the vapors are narcotic (see Section III-D, Toxicity - Birds and Mammals, p. 204).

Skin contact with liquid solvent or vapor may lead to dermatitis. The skin chaps due to the defatting activity and lipid solubility of the ketones (Rowe and Wolf, 1963; Smyth et al., 1949). Occupational dermal exposures are usually concurrent with inhalation of vapors; therefore, any physiological effects other than dermatitis may be due to the combined exposures.

1. Acute Exposure: Occupational and Related Contact

The majority of the ketonic solvents have not resulted in industrial incidents and injuries in their usage.

Smith and Mayers (1944) report additional cases in which inhalation and dermal exposures to methyl ethyl ketone have occurred in raincoat factories using methyl ethyl ketone (MEK) as a solvent. In one instance, the air concentrations of MEK ranged from 300 ppm to 600 ppm, and additional contact was made because the workers tended to wash their hands in the solvent. As a result of this exposure, several workers developed disabling dermatoses and/or numbness of the fingers and arms. One worker also complained of numbness in the legs. Smith and Mayers (1944) note that exposure of the face and other bare skin to vapors of MEK is enough to develop dermatitis if proper ventilation is not employed.

In the other incidents reported by Smith and Mayers (1944), the employees were exposed to a mixture of acetone and MEK, with concentrations of MEK ranging from 398 to 561 ppm and of acetone from 330 to 495 ppm. The combined effect of these two ketones led to gastric complaints, headaches, and fainting in two girls who were involved in brushing waterproofing materials, which were dissolved in the solvents, onto raincoats.

One other incident involving methyl ethyl ketone (MEK) was reported by Smyth (1956). An eye injury resulted from exposure to MEK vapor; however, the injury was believed to have been caused by an impurity and not the solvent itself.

Elkins (1959) reported headache, nausea, and respiratory irritation in workers exposed to methyl isobutyl ketone at a level of approximately 100 ppm. These symptoms were alleviated by installation of a better ventilation system which lowered concentration to about 20 ppm.

Specht and coworkers (1940) found that dermal exposures to mesityl oxide caused considerable irritation. During their experiments on animals, several laboratory workers complained of irritation of their hands even though they were wearing latex gloves.

One other ketonic solvent is reported to cause some gastritis in humans. Acetophenone, also known as hypnone, was used in the treatment of mental patients in the 19th century to sedate and induce sleep. The acetophenone was only of secondary importance as a sedative (Mairet and Comberbale, 1886), and at therapeutic levels, this ketone caused a burning sensation in the stomachs of some patients.

2. Chronic Exposures: Epidemiology of Peripheral Neuropathy

Clinical, histopathological, and electrophysiological evidence indicate that methyl n-butyl ketone produces a peripheral neuropathy in chronically exposed humans. In addition, 2,5-hexanedione, the principal body metabolite of MBK, the related alkane n-hexane, and the alcohol 2,5-hexanediol, each produce similar peripheral neuropathies in chronically exposed animals. The pathology which underlies this peripheral neuropathy is concurrent axonal degeneration of the distal regions of vulnerable nerve fibers sited in both the peripheral and central nervous systems. This type of pathology has been termed "dying-back" or "central and peripheral distal axonopathy" (Spencer and Schaumburg, 1976c-e). Certain compounds -- lead salts, acrylamide, organophosphates, thallium salts -- are only poisonous when gross overexposure occurs (Fullerton, 1969). Acrylamide, tri-ortho-cresyl phosphates, n-hexane, and certain nutritional disorders have all been found to cause a "dying-back" disease where a distal degeneration of nerve fibers occurs (Herskowitz et al., 1971; Schaumburg et al., 1974; Krishnamurti et al., 1972; Cavanagh, 1964). In the dying-back polyneuropathies, clinical signs of weakness occur bilaterally in distal regions of the legs and then proximally (Spencer and Schaumburg, 1974b). In the peripheral nervous system, nerve fiber degeneration commences in tibial nerve branches supplying the calf muscles and, in the central nervous system, in the distal regions of long nerve tracts located in the spinal cord, medulla oblongata, and cerebellum (Spencer and Schaumburg, 1976d, 1976e). Histological findings include axonal swellings with masses of neurofilaments, an increased number of mitochondria, myelin degeneration, and the presence of abnormal axonal organelles (Spencer and Schaumburg, 1974b).

A peripheral neuropathy similar to that described above has resulted from the practice of "huffing" (Prockop et al., 1974). "Huffing" of organic solvents is accomplished by inhaling vapors from solvent-soaked rags. No direct oral use or prolonged cutaneous contact with the liquid occurs. Severe cases of "huffing" neuropathy have been reported in seven men in Florida who had been using a commercially available lacquer thinner consisting of 11 compounds. At this writing, Prockup has not indicated what component or components are suspected as being neurotoxins. The lacquer thinner contained the following substances:

n-hexane	0.5%	(a known neurotoxin, see Schaumburg and Spencer, 1976)
acetone	12.7%	
isopropyl acetate	1.2%	
isopropyl alcohol	0.5%	
isobutyl acetate	12.6%	
toluene	3.9%	
isobutyl alcohol	3.5%	
isobutyrate	0.5%	
xylene	43.6%	
methyl amyl ketone	15.5%	
2-nitropropane	5.8%	

Tison and coworkers (1976) have stated that methyl amyl ketone, earlier suspected as the offending agent in "Huffer's" neuropathy (Means *et al.*, 1975) does not produce neuropathy in chronically exposed rats and chickens. Experimental neuropathy was produced by chronic exposure to the lacquer thinner.

In mid-August, 1973, an employee in the print department at an Ohio vinyl-coated fabrics plant was diagnosed as suffering from a peripheral neuropathy of suspicious origin (Gilchrist *et al.*, 1974; Billmaier *et al.*, 1974; Craft, 1974; Allen *et al.*, 1975). The patient complained of having been weak since May. His clinical symptoms included: bilateral weakness of the wrist extensors and flexors, and the finger extensors, flexors and abductors; a foot drop, bilateral atrophy of the interosseous muscles; and absence of ankle deep tendon reflexes. Results of an electromyogram (EMG) confirmed the diagnosis (Gilchrist *et al.*, 1974). According to the patient described above, five other employees in the print department of this plant were suffering from similar symptoms. Subsequently health officials performed EMG's on over 1,100 employees throughout the plant.

Data from this survey have been summarized by both Gilchrist and associates (1974) and Billmaier and coworkers (1974). Gilchrist and associates (1974) report that 45 cases of peripheral neuropathy which could not be attributed to non-occupational causes (e.g., diabetes) were found. Thirty-five of these cases appeared in print department workers. This is similar to the report by Billmaier and coworkers (1974) which included information in cases of neuropathy which could have been caused by diabetes or isoniazid therapy (see Table 66).

Table 66. Ill vs. Not Ill Employees, in Print Department and Non-Print Departments, Showing Job Categories in the Print Department (Billmaier *et al.*, 1974)

Group	Ill	Not Ill	Total
Non-Print Departments	30[*]	954	984
Print Department (Total)	38[†]	135	173
Operators[‡]	27	42	69
Helpers[‡]	10	49	59
Foremen		21	21
Service Helpers	1	15	16
Not Known		8	8
Total, All Departments	68	1089	1157

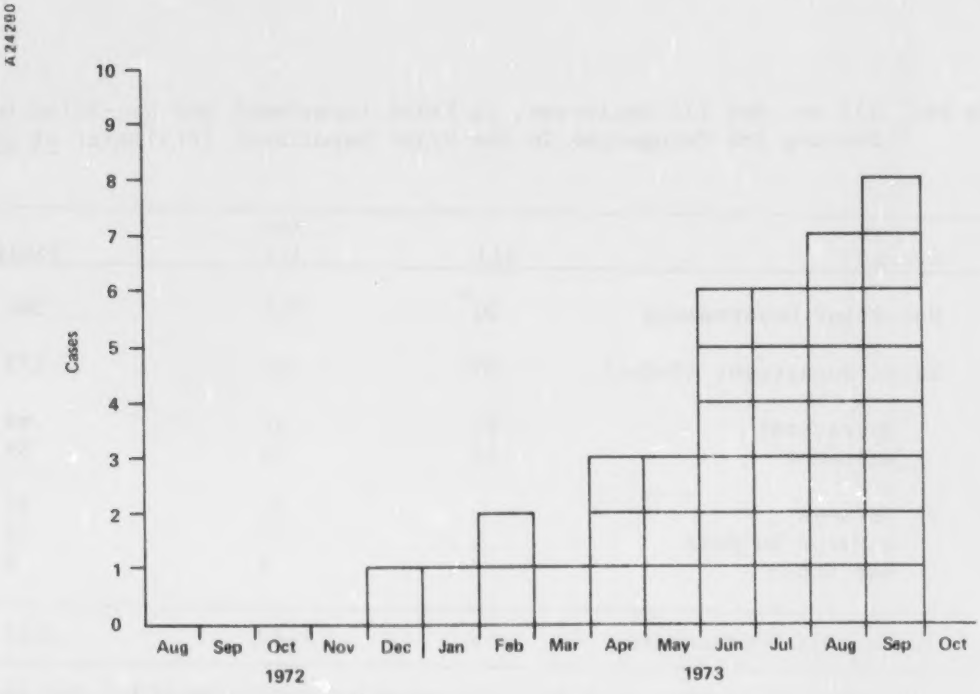
[*] Includes 18 persons with diabetes or other condition which can cause or contribute to neuropathy.

[†] Includes one person with diabetes, and one person on isoniazid therapy.

[‡] Significant at $p < .001$ using the chi-square test.

Investigation of the plant revealed that methyl *n*-butyl ketone (MBK) was introduced to the printing department in August, 1972, as a substitute for methyl isobutyl ketone (MIBK) in a solvent mixture with methyl ethyl ketone (MEK). By December 1972, MBK had completely replaced MIBK and at this time the first symptoms of neuropathy were occurring in the workers (see Figure 36).

Due to the predominance of cases of neuropathy in workers in the print department, chemical analysis of the vapors in the printing area were conducted. Contamination levels of MIBK, methyl methacrylate, *n*-hexane, toluene, xylene, methyl alcohol, acetone, and mineral spirits were very small (Billmaier *et al.*, 1974). The MEK and MBK levels, high in all areas, are given in Table 67. Although there is considerable variability in concentrations of the chemicals, the back of the printer had quite high vapor levels.



*Month of Onset for 7 Cases Unknown

Figure 36. Thirty-eight Peripheral Neuropathy Cases, by Month of Onset* in Ohio Factory Workers, December 1972 - September 1973 (Gilchrist *et al.*, 1974)

Table 67. Results of Area Atmospheric Sampling for Methyl Ethyl Ketone* (MEK) and Methyl Butyl Ketone** (MBK) in Parts Per Million (Billmaier *et al.*, 1974)
Data is listed from lowest to highest result obtained for each solvent at each work location.

	Front of Printer		Back of Printer		Wind-up Area	
	MEK	MBK	MEK	MBK	MEK	MBK
	104	2.3	85	2.5	39	1.0
	109	2.6	265	3.0	44	2.0
	124	4.1	401	9.0	47	2.0
	162	5.1	440	9.8	49	2.6
	220	5.8	603	21.7	127	5.9
	453	9.7	608	23.9	143	6.0
	565	11.5	725	48.6	250	7.9
	570	19.8	750	49.9	289	9.8
	670	21.7	763	156.0	338	17.5
Mean:	331	9.2	516	36.0	147	6.1

*Threshold Limit Value, MEK = 200 parts per million

**Threshold Limit Value, MBK = 100 parts per million

In addition to the presence of high amounts of vapors, poor working practices such as: (1) eating in the work area, (2) washing hands with the solvent, and (3) using solvent soaked rags to clean equipment were noted (Billmaier et al., 1974). These practices, as well as working overtime, increased the risk of disease (Gilchrist et al., 1974).

In September, 1973, the department was closed for installation of improved ventilation and removal of MBK from the production areas. Improved working practices were instituted before reopening the printing department. Since that time no new cases of peripheral neuropathy have been reported (Gilchrist et al., 1974), and once removed from the work environment, those affected by the disease have improved greatly (Allen et al., 1975). The recovery pattern of workers who had developed neuropathy is presented in Figure 37.

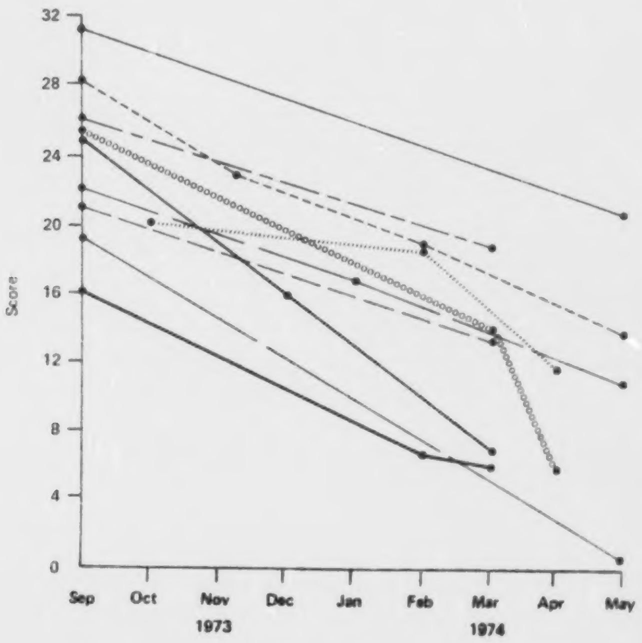


Figure 37. Rates of Recovery After Exposures Ceased, With Points Representing Total Scores of Clinical and EMG Findings (Allen et al., 1975)

The apparent rash of cases of neuropathy reported in Ohio tend to indicate that a change in production was responsible; over the past several years, the only change of that sort was the introduction of MBK into the work environment. A similar plant on the West Coast which has not used MBK has reported no incidents of disease (Craft, 1974). Craft (1974) has reported two isolated cases of peripheral neuropathy following occupational MBK exposure in Connecticut and Iowa. The information presented here, in conjunction with animal studies (see Section III-D-3), indicates that MBK exposure causes a toxic peripheral neuropathy in humans.

3. Controlled Studies

Few studies on the toxicity of ketonic solvents to humans have been conducted. The primary route of absorption utilized in these studies is inhalation (see Table 68), though some tests on skin sensitization have been reported.

a. Inhalation

Early investigators have determined intolerable or objectionable vapor levels for several of the ketones -- methyl ethyl ketone (Patty et al., 1935), methyl n-propyl ketone (Yant et al., 1936), methyl n-butyl ketone (Schrenk et al., 1936). In these three ketones the objectionable levels for a few minutes of exposure were 1000 ppm or greater. Specht and coworkers (1940) exposed subjects to lower concentrations and found that 150 ppm of methyl n-propyl ketone vapor caused eye, nose, and throat irritation.

Nelson and coworkers (1943) performed controlled vapor exposure tests on several solvents including methyl ethyl ketone and cyclohexanone. The same group of investigators conducted further studies of a similar experimental design of five other ketones -- methyl isobutyl ketone, diisobutyl ketone, diacetone alcohol, mesityl oxide, and isophorone -- a few years later (Silverman et al., 1946). Ten to twelve individuals (male and female) were exposed to solvent vapors at varying concentrations for three to five minute periods in a 1200 ft^3 chamber. After exposure, each person was asked to classify the effect of the solvent vapor on the eyes, nose, and throat as causing either: (1) no reaction, (2) slight irritation, or (3) strong irritation. The odor, if any, was classified as definite, moderate, strong, or overpowering. Then each person was asked if he felt he could work in the atmosphere for a full eight hours.

Table 68. Human Inhalation - Exposure Levels and Physiological Effects

Ketone	Level of Exposure (ppm)	Effects & Comments	Reference
Methyl ethyl ketone	100	Throat irritation	Nelson *et al.*, 1943
	200	Eye irritation	
	300	Objectionable - highest bearable level for 8 hr. day - 200 ppm	
	1000	Almost intolerable (short exposure)	Patty *et al.*, 1935
Methyl *n*-propyl ketone	150	Eyes, nose, throat irritation	Specht *et al.*, 1940
	1300	Objectionable to eyes and nose	
	1500	Markedly irritating to nose and eyes	Yant *et al.*, 1936
Methyl *n*-butyl ketone	1000	Objectionable, strongly irritating to eyes and nose	Schrenk *et al.*, 1936
Methyl isobutyl ketone	100	Headache, nausea	Elkins, 1959
	>100	Threshold for detection of odor	Shell Chemical Corp., 1957a
	>200	Objectionable, highest bearable level for 8 hr. day - 100 ppm	Silverman *et al.*, 1946
Diisobutyl ketone	>50	Objectionable, highest bearable level for 8 hr. day - 25 ppm	Silverman *et al.*, 1946
	50	Eyes and nose irritation	Carpenter *et al.*, 1953
	100	Dizziness, headache, lacrimation, intolerable level	
2,5-Hexanedione	NS	Irritation of mucous membranes	Browning, 1965
Diacetone alcohol	100	Objectionable, highest bearable level for an 8 hr. day - 50 ppm	Silverman *et al.*, 1946
Mesityl oxide	25	Eye irritation	Silverman *et al.*, 1946
	50	Objectionable, highest bearable level for an 8 hr. day - 25 ppm	
Cyclohexanone	50	Eye irritation	Nelson *et al.*, 1943
	75	Objectionable, highest bearable level for an 8 hr. day - 25 ppm	
Isophorone	25	Objectionable, highest bearable level for an 8 hr. day - 10 ppm	Silverman *et al.*, 1946

As indicated in Table 68, the isophorone vapors were considered the most irritating of all the ketonic solvents, with the highest level tolerable for an eight hour work day at 10 ppm (Silverman et al., 1946). Three others were given a 25 ppm limit as the highest tolerable -- cyclohexanone (Nelson et al., 1943), diisobutyl ketone and mesityl oxide (Silverman et al., 1946).

Due to the design of these experiments, primarily subjective judgments on the vapor effects could be obtained since the exposures were only for a few minutes. The effects of general tolerance, decreased sensitivity of mucous membranes, or hypersensitivity could not be measured. At best the data presented can only give a rough idea of the irritation of these compounds.

Carpenter and associates (1953) exposed humans to longer periods of vapor exposures to verify the data presented by Silverman and coworkers (1946) on diisobutyl ketone. Initially Carpenter and coworkers (1953) exposed two men, 25 and 32 years old, to 50 ppm for a three hour period in a 6½ foot cube where the air was drawn in at approximately 900 ℓ/minute. At the beginning the men noted a slight irritation of eyes and nose. The vapor could be smelled and tasted throughout the exposure period. However, no appreciable discomfort was experienced. Ten days later these two men and one additional man were exposed to 100 ppm for three hours; these men all agreed that the 100 ppm exposure level would be unsatisfactory over an eight hour day. At this exposure level, slight lacrimation, dizziness, and headache were noted in addition to initial irritation (Carpenter et al., 1953).

Imasheva (1966) studied the effects of acetophenone inhalation in a group of 18 "practically healthy" people from age 18 to 20. For each individual a threshold of olfactory sensation was determined. The most sensitive person had a threshold at 0.202 ppb acetophenone. For the majority (14) of those tested, 0.404 ppb was the average threshold.

Three subjects were also tested for light sensitivity during exposure to acetophenone vapor. The threshold for decrease in light sensitivity was determined to be 0.202 ppb (Imasheva, 1966).

Dobrinskiy (1966) had determined the same threshold levels in fifteen individuals exposed to cyclohexanone vapors. With this ketone the threshold for olfactory sensation occurs at 53.2 ppb. The three persons involved in light studies suffered a decrease in sensitivity at a threshold concentration of 29.3 ppb (Dobrinskiy, 1966).

Dobrinskiy (1966) also studied the effects of cyclohexanone on brain activity in six human subjects. In this part of the experiment the subject was at relative rest during the exposure and then tested for conditional reflex and for reinforced rhythm with a flickering light. The threshold limit for effects of cyclohexanone on rhythm reinforcement as determined by electroencephalogram (EEG) was 22.4 ppb. In conditioned reflex, the threshold concentration was 14.9 ppb. On the basis of this information Dobrinskiy (1966) concluded that 9.9 ppb cyclohexanone should be the maximum permissible concentration for single exposure.

The variance in allowable vapor exposure determined in these studies is due to the difference in the criteria of the investigators Nelson and coworkers (1943) were concerned with determining the maximum concentrations of the chemical in workroom air which could be tolerated for eight hours, whereas the work on cyclohexanone by Dobrinskiy (1966) and acetophenone by Imasheva (1966) was more concerned with what levels actually caused some measurable effect.

The odor threshold of diacetone alcohol in water or room temperature, determined by using nine individuals, was found to range from 5.63 to 269 ppm with a mean of 44.12 ppm at room temperature (Lillard and Powers, 1975).

Methyl ethyl ketone, at vapor concentrations of 90 to 270 ppm for exposure periods of 0.5 to 4 hours, has been shown to affect estimates of time passage in both men and women. In men, time estimates were shortened, while in women, an increased variability in estimates of 5, 10, and 30 second time periods was found (Nakaaki, 1974). As noted earlier in this section, this type of exposure could create a secondary hazard in occupational situations.

b. Dermal

Ethyl n-amyl ketone and acetophenone were tested at a concentration of 2% in petrolatum on human skin. No irritation resulted from a 48 hour closed patch test in 25 subjects exposed to ethyl n-amyl ketone (Kligman, 1972) or a similar group exposed to acetophenone (Kligman, 1971). Further tests did not indicate any sensitization had occurred in either case. Katz (1946), however, has called acetophenone a common skin irritant.

D. Toxicity - Birds and Mammals

1. Acute Toxicity

a. Acute Oral Toxicity

Numerous studies have been conducted on the acute oral toxicity of the ketonic solvents. Some of the essential experimental details and basic lethality data from these studies are summarized in Table 69. Most of this information comes from the work of Smyth, Carpenter, and coworkers at the Mellon Institute. Where two references are given for a single entry -- e.g, methyl _n_-propyl ketone -- the first refers to a relatively detailed but unpublished Mellon Institute report, while the latter refers to summaries of these reports periodically published in range-finding toxicity data lists. Direct references to Mellon Institute cite unpublished summary data sheets or monthly reports from that institution. Because the same general methodology was followed in all of these studies, an evaluation of the comparative toxicities of the ketones is somewhat facilitated.

As Smyth and coworkers have emphasized repeatedly, these studies are designed only to estimate comparative hazards (Smyth and Carpenter, 1948; Smyth _et_ _al_., 1954 and 1962). The results are most often expressed as 14 day LD_{50}'s ± 1.96 standard deviations. These results are usually based on four to six dose levels of the compounds administered to groups of six to ten animals. Mortality is noted over the ensuing fourteen days, and the statistical methods of Thompson (1947) and Weil (1952) are used in estimating the LD_{50}'s (Smyth _et_ _al_., 1962).

Table 69. Acute Oral Toxicity of Various Ketones: Single Dose by Intubation

Chemical	Dilution and Vehicle	Organism*	Number Treated per Dose Level	Dose (g/kg)	Mortality Data	Reference
Saturated Aliphatics						
# Carbons						
3 Acetone	n.s	Rats, F, C-W (4-5)	n.s.	10.7 (7.3-14.1)	14 day LD_{50} (±1.96 S.D.)	Smyth et al., 1962
4 Methyl ethyl ketone	10% dispersion in 1% "Tergitol" 7**	Rats, M, Sh	10	3.98# (3.94-4.01)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1949
	n.s.	Rats	n.s.	3.3	Lethal	Shell Chemical Corp., 1959
	n.s.	Rats, F, C-W (4-5)	5	5.53 (4.50-6.82)	14 day LD_{50} (±1.96 S.D.)	Smyth et al., 1962
5 Methyl n-propyl ketone	10% dilution in corn oil	Rats, M, C-W (5-6)	5	3.73# (2.68-5.21)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1954 (Smyth et al., 1962)
Diethyl ketone	n.s.	Rats, M, C-W (3-4)	5	2.14 (1.54-2.99)	14 day LD_{50} (±1.96 S.D.)	Smyth et al., 1954
6 Methyl n-butyl ketone	n.s.	Rats, M, C-W (3-4)	5	2.59 (2.11-3.18)	14 day LD_{50} (±1.96 S.D.)	Smyth et al., 1954
Methyl isobutyl ketone	n.s.	Rats, M	n.s.	4.57	LD_{50}	Union Carbide, 1968
	20% in 1% "Tergitol" 7	Rats, F, C-W (3-4)	n.s.	2.08 (1.91-2.27)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute 1953
7 Methyl n-amyl ketone	20% in 1% "Tergitol" 7	Rats, F, C-W (3-4)	n.s.	1.67 (1.48-1.88)	14 day LD_{50} (±1.96 S.D.)	Smyth et al., 1962
Methyl isoamyl ketone	undiluted	Rats, M, CFN (5-6)	5	3.48# (2.12-5.66)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1957 (Smyth et al., 1962
Ethyl n-butyl ketone	20% in 1% "Tergitol" 7	Rats, M,W	n.s.	2.76# (2.56-2.98)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1948a (Smyth et al., 1949)
8 Ethyl n-amyl	n.s.	Rats	n.s.	>5	LD_{50}	Shelanski, 1973
Ethyl sec-amyl ketone	n.s.	Rats Guinea Pigs Mice	n.s. n.s. n.s.	3.5 2.5 3.8	LD_{50} LD_{50} LD_{50}	Shell Chemical Corp., 1958
9 Diisobutyl ketone	20% in 1% "Tergitol" 7	Rats, M,W	10	5.75 (4.69-7.06)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1948b (Smyth et al., 1949)
12 Isobutyl heptyl ketone	20% in 1% "Tergitol" 7	Rats, M,W	10	8.74 (7.18-9.99)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1948c (Smyth et al., 1949)
Other Saturated						
2,4-Pentanedione	10% in water	Rats, M,W	10	1.05	14 day LD_{50}	Smyth, 1941a (Smyth & Carpenter, 1944)
	5% in water	Rats, M,W (3-4)	10	0.97# (0.90-1.05)	14 day LD_{50} (±1.96 S.D.)	Smyth, 1945
	n.s.	Rabbits	n.s.	0.94 (0.84-1.07)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute 1955
2,5-Hexanedione	n.s.	Rats, M, W (3-4)	n.s.	2.7	14 day LD_{50}	Smyth & Carpenter, 1944
Diacetone alcohol	10% in water	Rats, M,	n.s.	4.0	14 day LD_{50}	Smyth, 1946a

Table 69. (cont'd)

Chemical	Dilution and Vehicle	Organism*	Number Treated per Dose Level	Dose (g/kg)	Mortality Data	Reference
Unsaturated Aliphatics						
Methyl isopropenyl ketone	n.s.	Rats	n.s.	0.18	LD_{50}	Rowe & Wolf, 1963
	n.s.	Guinea Pigs	n.s.	(0.06-0.25)	Lethal range	
Mesityl oxide	20% in 1% "Tergitol" 7	Rats, M,W (3-4)	10	1.12 (0.99-1.28)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute, 1952
	20% in 1% "Tergitol" 7	Guinea Pigs	10	1.0#	Lethal to 6 animals within 14 days	Carpenter, 1941
Alicyclics & Aromatics						
Cyclohexanone	undiluted	Rats, M,W (3-4)	5	1.54# (1.14-2.08)	14 day LD_{50} (±1.96 S.D.)	Nycum et al., 1967 (Smyth et al., 1969a)
	n.s.	Rats, F	n.s.	1.34	14 day LD_{50}	" "
	undiluted	Mice	n.s.	1.4	LD_{50}	Novogorodova et al., 1967
	undiluted	Rabbits, "young"	3	1.6-1.9	LD_{100}	Treon et al., 1943a
	n.s.	Mice		2 78	24 hour LD_{50}	Caujolle & Caujolle, 1965
Methycyclohexanone	undiluted	Rabbits "young"	5	1.25-5.0	LD_{100}, all animals died in 14-90 min.	Treon et al., 1943a
Isophorone	n.s.	Rats	n.s.	1.87	LD_{50}	Union Carbide, 1968
	undiluted	Rats, F,W	5	2.10	14 day LD_{50}	Smyth et al., 1969b
	n.s.	Rats, F,W	5	2.12	14 day LD_{50}	Smyth et al., 1970
Acetophenone	n.s.	Rats	n.s.	3.0	14 day LD_{50}	Smyth & Carpenter, 1944
	20% in 1% "Tergitol" 7	Rats, M,W (3-4)	10	0.9 (0.81-1.00)	14 day LD_{50} (±1.96 S.D.)	Smyth, 1946b (Smyth et al., 1949)
	undiluted	Rats, M,W (3-4)	n.s.	2.20 (1.59-3.10)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute, 1956
	propylene glycol	Rats, F	n.s.	1.07	14 day LD_{50}	Mellon Institute, 1956
	corn oil	Rats, F	n.s.	5.20	14 day LD_{50}	
	n.s.	Rats, M/F, O-M	10 (SM,SF)	3.200 (2.460-4.160)	14 day LD_{50}	Jenner et al., 1964
	n.s.	Rabbits	n.s.	1.76 (1.67-1.85)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute, 1956
	undiluted	Rats, F,W	5	2.55	14 day LD_{50}	Smyth et al., 1969b
Benzophenone	n.s.	Rats	n.s.	>10	LD_{50}	Opdyke, 1973

KEY: *The following data is included when available.

Animal, Sex (M/F), Strain of Rats [C-W, Carworth-Wistar; CFN, Carworth Farms-Nelson; O-M, Osborne-Mendel; W, Wistar derived], all animals of these strains weighed between 90-120g, Age of animal in weeks given in parenthesis.

**"Tergitol" Penetrant 7: an aqueous solution of 25% sodium 3,9-diethyl-6-tridecanol sulfate used as a dispersing agent (Smyth et al., 1962). Oral 14 day LD_{50} for rats of 5.66 g/kg (4.85-6.60) Smyth and Carpenter, 1948.

# Dose response data available, see Table 70.

n.s. = not specified

Dose-response information is available on nine of the ketonic solvents under review and is summarized in Table 70. All of these ketones appear to have a relatively low LD_{100} to LD_0 ratio. For methyl ethyl ketone and ethyl n-butyl ketone, the LD_{100}/LD_0 is only two. The highest LD_{100}/LD_0 is four, given by both methyl n-propyl ketone and cyclohexanone. Given these narrow ranges between complete and zero lethality, it is not surprising that four of these ketones -- ethyl n-butyl ketone, diisobutyl ketone, mesityl oxide, and acetophenone -- do not show consistent positive correlations between dose and mortality.

Table 70 : Per Cent Mortality in Rats After Intubation With Various Ketonic Solvents (see Table for reference and experimental details)

	Dose of Ketone in g/kg								
Ketone Mortality	Methyl ethyl Ketone	Methyl n-propyl Ketone	Methyl isoamyl Ketone	Ethyl n-butyl Ketone	Diisobutyl Ketone	2,4-Pentanedione	Mesityl oxide	Cyclo-hexanone	Aceto-phenone
100%	6.3	7.95		3.98		1.58		3.8	
90%	5.0			2.52					
80%			5.84		7.95			1.9	1.26
70%					5.0				0.87
60%	3.98	3.98				1.26	1.0		1.0
50%									
40%			2.92						
30%					3.98	1.0			
20%				3.16	6.3		0.5 ± 0.63		0.63
10%							0.795		0.795
0%	3.16	2.00	1.46	2.00		0.5		0.95	
LD_{50} (±1.96 S.D.)	3.98 (3.96-4.01)	3.73 (2.68-5.21)	3.48 (2.12-5.66)	2.76 (2.56-2.98)	5.75 (4.69-7.06)	0.97 (0.90-1.05)	-	1.54 (1.14-2.08)	0.90 (0.81-1.00)

At sufficiently high doses, all of the ketonic solvents seem to have about the same pharmacologic effect: profound narcosis with central nervous system depression. Based on the available data, narcosis is apparently rapid in onset. Nonfatal doses of both cyclohexanone (0.89 - 1.6 g/kg) and methylcyclohexanone (0.56 - 1.0 g/kg) caused narcosis in rabbits within 4-30 minutes and 30-60 minutes, respectively. Generally, the period to onset of narcosis is inversely proportional to the dose. The duration of narcosis in these exposures is relatively prolonged, lasting from seven to fifteen hours (Treon _et al_., 1943a). This is similar to the activity of methyl ethyl ketone, which at levels above the LD_{50} (≃ 4 g/kg) caused narcosis for as long as fifteen hours in surviving rats (Carpenter, 1949). In fatal exposures, death usually occurs within forty-eight hours of dosing. As with the onset of narcosis, death usually occurs more rapidly at higher doses. Detailed data on methyl ethyl ketone in Table 71 illustrates this pattern.

Table 71. Response of Rats to Single Intubations of Methyl Ethyl Ketone (from Carpenter, 1949)

Dose	Mortality	Number of Dying on Specified Day After Dosing			
(g/kg)	(# dying/# exposed)	Day 0	Day 1	Day 2	Day 6
3.16	0/10				
3.98	6/10	1	4		1
5.0	9/10	2	6	1	
6.3	10/10	3	7		

Only with trimethylnonanone is delayed death noted. With this ketone, death usually does not occur until seventy-two hours after dosing (Carpenter, 1948c).

Gross pathological findings are also quite similar in ketone intoxication. Congestion or hemorrhage of the lungs, congestion of the liver and intestines, as well as discoloration of the liver, kidney, and spleen are most often noted. In addition, methyl _n_-propyl ketone has caused surface burns on the liver where contact with the stomach occurred (Carpenter, 1954), and ethyl _sec_-amyl ketone has caused local irritation of the gastric mucosa in rats, guinea pigs, and mice (Shell Chemical Corp., 1958).

As is evident in Table 69, the commercially significant ketonic solvents have a relatively narrow range of acute oral toxicity. Fourteen day LD_{50}'s range from about 1 g/kg for 2,4-pentanedione, mesityl oxide, and acetophenone to about 10 g/kg for acetone and trimethylnonanone. Only methyl isopropenyl ketone (LD_{50} 0.18 g/kg to rats) falls outside of these limits. Further, the confidence limits of the LD_{50} estimates given in Table 69 sometime approach a factor of two [e.g. - methyl *n*-propyl ketone, LD_{50} (± 1.96 S.D.) of 3.73 (2.68-5.21) g/kg], making precise comparisons of toxicity among the various ketones difficult. However, in terms of relative toxicity, the ketones do seem to fall into three basic groups: those with 14 day LD_{50}'s near or below 1 g/kg, those with LD_{50}'s between 1 and 5 g/kg, and those with LD_{50}'s above 5 g/kg. Using this rather arbitrary classification, a semi-quantitative comparison of the acute oral toxicity of the various ketones is offered in Table 72.

Table 72. Relative Acute Oral Toxicity of the Ketonic Solvents
(based on data from Table 69)

	Relatively High Toxicity (1)	Medium Toxicity (2)	Relatively Low Toxicity (3)
more	Methyl Isopropenyl ketone	Cyclohexanone	Ethyl *n*-amyl ketone
toxic	2,4-Pentanedione	Methyl *n*-amyl ketone	Diisobutyl ketone
↑	Acetophenone	Isophorone	Trimethylnonanone
	Mesityl oxide	Methyl isobutyl ketone	Acetone
	Methylcyclohexanone	Methyl *n*-butyl ketone	
		2,5-hexanedione	
less		Ethyl *n*-butyl ketone	
toxic		Methyl isoamyl ketone	
		Methyl *n*-propyl ketone	
		Methyl ethyl ketone	
		Diacetone alcohol	

(1) 14 day LD_{50} approximately 1 g/kg or below
(2) 14 day LD_{50} 1-5 g/kg
(3) 14 day LD_{50} generally above 5 g/kg

While this type of classification may well do the least violence to the available data, it is not particularly satisfying. However, before more detailed comparisons can be made, some of the experimental parameters which may affect estimates of ketone toxicity should be appreciated. Information is available on four of these parameters: the vehicle used in administering the ketone, and the sex, species, and age of the animal used.

Of all the factors affecting the oral toxicity of a given ketone, the vehicle used in administering the ketone seems to be the most important. This is particularly evident in the studies on acetophenone summarized in Table 69. For female rats, the LD_{50}'s varied from 1.07 g/kg using propylene glycol as the vehicle to 5.20 g/kg using corn oil (Mellon Institute, 1956). Undiluted acetophenone has an intermediate LD_{50}, 2.25 g/kg, for female rats (Smyth et al., 1969b). Similar variations are seen in male rats of the same strain and age, with undiluted acetophenone having a 14 day LD_{50} of 2.20 g/kg but a 20% dispersion of acetophenone in 1% "Tergitol" 7 being about twice as toxic -- 14 day LD_{50} of 0.9 g/kg (Mellon Institute, 1956; Smyth, 1946b). The toxicity of acetone is also influenced by the vehicle used. Rats -- presumably of the same sex and strain -- yielded an LD_{50} of 12.2 (8.0 - 18.8) g/kg with undiluted acetone and a LD_{50} of 9.15 (8.9 - 9.9) g/kg with 50% acetone in water (Mellon Institute, 1965; data not summarized in Table 69). Although comparable data is not available for the other ketones, it seems reasonable to assume that the vehicle has a significant effect on oral ketone toxicity by influencing the amount absorbed and/or rate of absorption.

Although rats have been most often used in acute oral toxicity studies, tests have also been conducted using rabbits, mice and guinea pigs. Consequently, LD_{50} values are available on rats and at least one of these other animals for ethyl sec-amyl ketone, 2,4-pentanedione, methyl isopropenyl ketone mesityl oxide, cyclohexanone, and acetophenone (see Table 69). For most of these ketones, the LD_{50} values are extremely close. The greatest apparent difference in species response is found with ethyl sec-amyl ketone (guinea pig LD_{50} of 2.5 g/kg, rat 3.5 g/kg, mice 3.8 g/kg). However, these values are well within the limits of variation often noted in testing different groups of rats -- e.g., acetophenone and methyl ethyl ketone. Thus, none of these common laboratory mammals seem particularly sensitive to ketone ingestion. This has been specifically noted by Novogorodova and coworkers (1967) who, while providing no experimental details, state that rats and rabbits are no less susceptible than mice to oral doses of cyclohexanone.

The effect of age on the susceptibility to ketone poisoning has been examined for methyl ethyl ketone using Sprague-Dawley rats of three age groups: 14 days old (16-50 g), young adult (80-160 g), and older adult (300-470 g). The acute oral LD_{50}'s (with 95% confidence limits) for these groups were 2.5 (2.0-3.2) g/kg, 2.9 (2.3-3.5) g/kg, and 2.7 (2.1-3.5) g/kg, respectively. These results indicate that methyl ethyl ketone is isotoxic in all three age groups (Kimura et al., 1971). No additional information is available on the effect of age on ketone toxicity.

The effects of sex on the response to the oral administration of ketones is unclear. Information is available on the responses of both male and female rats to methyl ethyl ketone, methyl isobutyl ketone, and acetophenone (see Table 69 for details). Based on the LD_{50} values given, males seem more sensitive to methyl ethyl ketone and less sensitive to methyl isobutyl ketone than do female rats. However, the vehicles used in the female methyl

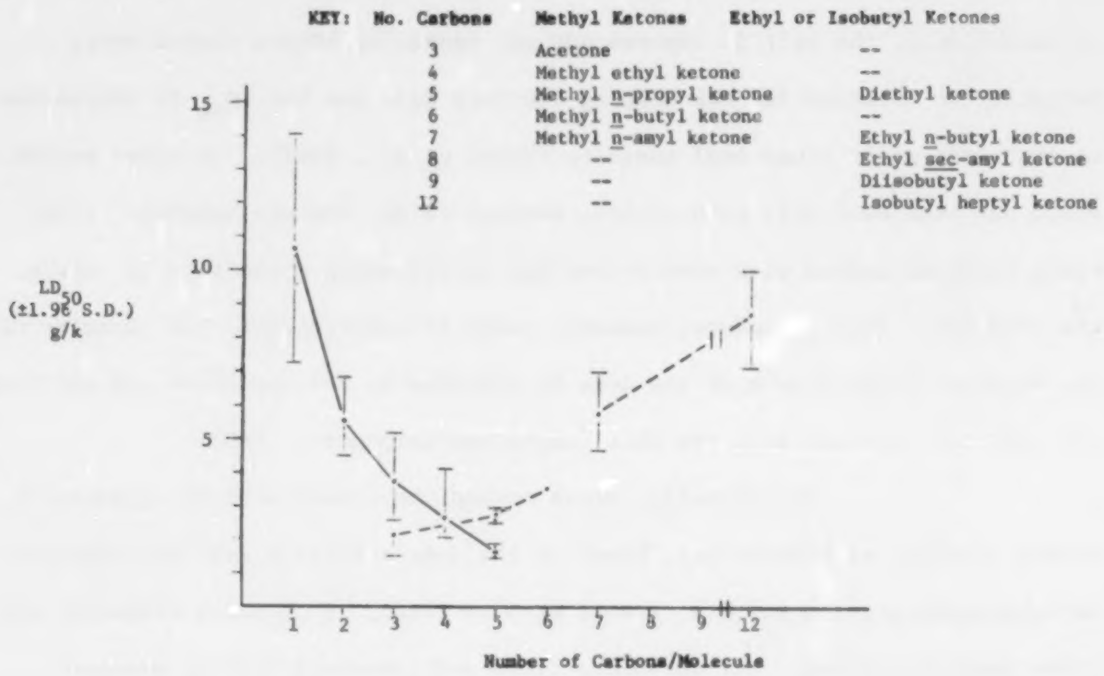
ethyl ketone study and male methyl isobutyl ketone study are not specified. For acetophenone, the undiluted ketone has about the same LD_{50} values for both male (2.2 g/kg) and female (1.76 g/kg) rats. Consequently, the apparent difference in the responses of males and females to methyl ethyl ketone and methyl isobutyl ketone may possibly be attributable to differences in the vehicles used.

Thus, of the four experimental parameters on which some information is available, the type of vehicle used seems to have a marked effect on estimates of ketone oral toxicity. The type of common laboratory mammal (rat, mouse, rabbit, or guinea pig) used seems to have no pronounced effect. The influences of age and sex on susceptibility to ketone intoxication is less clear. The limited information available does not indicate that sex and age have pronounced effects in the response of rats.

Given these limitations, certain patterns do seem evident in the acute oral toxicities of the ketonic solvents. Rowe and Wolf (1963) have stated that ketone toxicity generally increases with increasing molecular weight. This does seem to apply to the acute oral toxicities of the straight chain methyl ketones with three to seven carbons. However, the reverse relationship seems apparent in the acute oral toxicities of ethyl and isobutyl ketones of five to twelve carbons. Both of these patterns are illustrated in Figure 38.

In an attempt to make this comparison as reliable as possible, the LD_{50} values given by Smyth, Carpenter and associates are used when available in Figure 38. Only the LD_{50} value for ethyl sec-amyl ketone is from another source -- i.e., Shell Chemical Corporation, 1958. The choice of the LD_{50} value for methyl ethyl ketone used in Figure 38, 5.53 g/kg (Smyth et al., 1962), is arbitrary. The value given by Carpenter (1949), 3.98 g/kg, could be used with equal justification.

If the ketones in Figure 38 are considered as a single series, a roughly parabolic relationship between acute oral toxicity and molecular weight is apparent. This is similar to the patterns noted for a series of alicyclic ketones (Caujolle and Caujolle, 1965) and acyclic aliphatic ketones (Jeppsson, 1975) on intraperitoneal and intravenous injections (see Figure 40, p. 244).



KEY: No. Carbons	Methyl Ketones	Ethyl or Isobutyl Ketones
3	Acetone	--
4	Methyl ethyl ketone	--
5	Methyl n-propyl ketone	Diethyl ketone
6	Methyl n-butyl ketone	--
7	Methyl n-amyl ketone	Ethyl n-butyl ketone
8	--	Ethyl sec-amyl ketone
9	--	Diisobutyl ketone
12	--	Isobutyl heptyl ketone

Figure 38. Relationship Between Number of Carbons per Molecule and Acute Oral LD_{50}'s With Rats for Straight Chain Methyl Ketones (•———•) and Ethyl or Isobutyl Ketones (•----•) (See Table 69 for sources of data and experimental details.)

b. Acute Dermal Toxicity

As indicated in Table 73, many of the ketonic solvents have been tested for acute dermal toxicity. As with oral toxicity, most of the studies have been conducted by Smyth, Carpenter, and coworkers at the Mellon Institute. The basic techniques used in these studies is the one-day cuff method. This involves clipping the fur from the entire trunk of male albino New Zealand rabbits. The ketone is then applied to the skin and a sheet of impervious plastic film (or cuff) is used to keep the dose in contact with the skin. After twenty-four hours, during which time the rabbit is immobilized, the cuff is removed and any remaining ketone washed away. Mortality is observed for the ensuing fourteen days and the LD_{50} is calculated as discussed under acute oral toxicity (Smyth et al., 1962). An older method -- which has been used only with diones, mesityl oxide, and acetophenone -- entails exposing guinea pigs over a four-day period using a poultice to retain the chemical. This procedure, however, tends to underestimate the toxicity of the chemical because much of the dose is absorbed by the saturated pad and does not come into contact with the skin (Smyth and Carpenter, 1948).

Occasionally, other methods have been used to estimate the dermal toxicity of ketones but, based on the data available for cyclohexanone and acetophenone, the results of such studies cannot be reliably compared with those described above. For instance, Treon and coworkers (1943a) applied 30 ml and 55 ml of cyclohexanone in 5 ml portions at 20 minute intervals to the skin of rabbits. Twenty minutes after the last application, the skin was washed with soap and water. Consequently, the cyclohexanone was in contact with the skin for under four hours. The rabbits receiving the smaller

Table 73. Acute Dermal Toxicity of Ketones

Compound	Organism	Number Exposed per Dose Level	Dose (g/kg)	Mortality	Reference
Simple Saturated Aliphatics					
Methyl ethyl ketone	Rabbit	4	8.1	14 LD_{50}	Smyth *et al.*, 1962
	Rabbit	3-10	10.2	14 LD_{50}	Carpenter, 1949
Methyl *n*-propyl ketone	Rabbit	4	6.5 (2.9-14.4)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1954 (Smyth *et al.*, 1962)
Diethyl ketone	Rabbit	4	16.2	14 day LD_{50}	Smyth *et al.*, 1954
Methyl *n*-butyl ketone	Rabbit	4	4.85 (3.44-6.80)	14 day LD_{50} (±1.96 S.D.)	Smyth *et al.*, 1954
Methyl isobutyl ketone	Rabbit	4	16.0	no mortality over 14 days	Mellon Institute, 1953
Methyl *n*-amyl ketone	Rabbit	4	10.3 (7.6-13.9)	14 day LD_{50} (±1.96 S.D.)	Smyth *et al.*, 1962
Methyl isoamyl ketone	Rabbit	4	8.8 (6.0-13.1)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1957 (Smyth *et al.*, 1962)
Ethyl *n*-butyl ketone	Rabbit	6	16.3	no mortality over 14 days	Carpenter, 1948a (Smyth *et al.*, 1949)
Ethyl *n*-amyl ketone	Rabbit	n.s.	>5	LD_{50}	Shelanski, 1973
Diisobutyl ketone	Rabbit	6	16.2	14 day LD_{50}	Carpenter, 1948b (Smyth *et al.*, 1949)
Isobutyl heptyl ketone	Rabbit	9-10	9.0 (7.7-10.6)	14 day LD_{50} (±1.96 S.D.)	Carpenter, 1948c (Smyth *et al.*, 1949)
Other Saturated Aliphatics					
2,4-Pentanedione	Rabbit	n.s.	4.85	approximate LD_{50}	Smyth, 1945
	Guinea Pig	n.s.	1.0	no deaths	Smyth, 1941a
2,5-Hexanedione	Guinea Pig	6	6.4	14 day LD_{50}	Smyth and Carpenter, 1944
Diacetone alcohol	Rabbit	n.s.	13.6 (12.8-14.6)	14 day LD_{50} (±1.96 S.D.)	Smyth, 1946a (Smyth and Carpenter, 1944)
Unsaturated Aliphatics					
Methyl isopropenyl ketone	Rabbit	6	0.20 (0.06-0.66)	14 day LD_{50} (±1.96 S.D.)	Smyth *et al.*, 1951
Mesityl oxide	Guinea Pig	6-10	1.9	14 day LD_{50}	Carpenter, 1941
	Mice	10	0.43	All dead in 3-9 hours	Shell Chemical Corp., 1957b
Alicyclic & Aromatic					
Cyclohexanone	Rabbit	4	0.948 (0.596-1.54)	14 day LD_{50} (±1.96 S.D.)	Nycum *et al.*, 1967 (Smyth *et al.*, 1967)
	Rabbit	n.s.	10.2-23.0	Lethal range	Treon *et al.*, 1943a
Methylcyclohexanone	Rabbit	n.s.	4.9-7.2	Lethal range	Treon *et al.*, 1943a
Isophorone	Rabbit	n.s.	1.39	LD_{50}	Union Carbide, 1968
Acetophenone	Rabbit	5-10	6.17 (5.19-7.36)	14 day LD_{50} (±1.96 S.D.)	Smyth, 1946b
	Rabbit	n.s.	16.3 (11.1-2.42)	14 day LD_{50} (±1.96 S.D.)	Mellon Institute, 1956
	Guinea Pig	6	20.3	No lethality over 14 days	Smyth and Carpenter, 1944
Benzophenone	Rabbit	n.s.	3.5 (2.0-6.2)	LD_{50}	Opdyke, 1973

portion -- which amounted to 10.9 g/kg -- became slightly anesthetized but survived. The other rabbit -- which received a dose of 23.1 g/kg -- died after three hours and forty-five minutes. Thus, the lethal range was estimated at 10.2 - 23.0 g/kg. The LD_{50} value estimated by Nycum and coworkers (1967) is about ten-fold lower than the non-lethal dose in the above exposure. Nycum and coworkers (1967), however, used the standard one-day cuff technique in which the animal was exposed to the cyclohexanone over a twenty-four hour period. This longer exposure period probably accounts for the much lower estimate of lethal dose.

Variations in exposure technique also seem to account for the various estimates of acetophenone dermal toxicity. The lack of mortality with guinea pigs at 20.5 g/kg (Smyth and Carpenter, 1944) is probably due to the use of the poultice in retaining the dose. As discussed previously, this technique is thought to give lower estimates of toxicity than the one day cuff method (Smyth and Carpenter, 1948). This is apparently true with acetophenone in that the standard one-day cuff method yielded a 14-day LD_{50} of 16.3 g/kg. In the third study which gave an even lower LD_{50} estimate of 6.17 g/kg, Smyth (1946b) applied varying doses of acetophenone to rabbit skin by gentle rubbing. Smyth (1946b) states that this method generally yields an LD_{50} about twice that of the cuff method. Thus, an LD_{50} of 3.08 g/kg was estimated as being comparable to an LD_{50} using the cuff method. This value, however, is not in agreement with the actual cuff LD_{50} of 16.3 g/kg (Mellon Institute, 1956). Assuming that no extraneous factors are involved, this discrepancy seems to support the conclusion that results based on different exposure techniques cannot be compared with satisfactory reliability. Thus, in Table 73, the data on benzophenone (Opdyke, 1973), ethyl n-amyl ketone (Shelanski, 1973), and isophorone (Union Carbide, 1968) are of limited use in estimations of comparative toxicity. This is particularly true for the estimates of Shelanski (1973) and Opdyke (1973), neither of which present any procedural details.

Methyl isobutyl ketone and ethyl n-butyl ketone are clearly among the least toxic on dermal application. These ketones are apparently absorbed slowly -- if at all -- and are not lethal to rabbits at the highest dose level which can be administered by the cuff technique. Details in the ethyl n-butyl ketone exposure indicate that this ketone caused neither skin irritation nor weight loss in exposed animals (Mellon Institute, 1953; Carpenter, 1948a). Diisobutyl ketone is also poorly absorbed and has a calculated LD_{50} near the maximum dose level, 16.2 g/kg.

Diacetone alcohol and acetophenone also have 14-day LD_{50} values above 10 g/kg by the standard cuff method. However, these ketones differ from the above group in terms of skin irritation. Diacetone alcohol causes erythema and shallow scaling in rabbits at doses near the LD_{50} (Smyth, 1946a). Acetophenone, which is even less toxic in 14 day mortality studies, causes severe skin necrosis which is typical of the more highly toxic ketones. In addition, acetophenone caused severe kidney damage (Smyth, 1946a).

Most of the other ketones on which data are available seem to be both toxic and corrosive at doses below 10 g/kg. Mesityl oxide is the most extensively studied of this group. In guinea pigs, doses from 1.85 to 3.98 g/kg caused rapid deaths in most animals and subcutaneous edema at the application site. Gross pathological observations included mottled liver, pale spleen and kidneys, as well as congestion of the stomach and intestines (Carpenter, 1941). The LD_{50} calculated for guinea pigs (1.9 g/kg) is well below the 5.13 g/kg LD_{50} for rabbits (Mellon Institute, 1952). In that the guinea pig poultice exposures presumably underestimate toxicity, these results could be interpreted as indicating that guinea pigs are more susceptible than rabbits to dermal applications of mesityl oxide. Mice, at least, do seem to be the most susceptible animal tested. On applications of only 0.43 g/kg, the skin became markedly irritated in a few minutes and narcosis was induced within fifteen minutes followed by death in three to nine hours (Shell Chemical Corp., 1957b). Methyl ethyl ketone, methyl n-propyl ketone, and methyl isoamyl ketone seem to have effects similar to those of mesityl oxide. Pathological findings for these ketones show involvement of the liver and kidneys along with erythema and narcosis of the skin. In addition, congestion and hemorrhage of the lungs were noted for both methyl isoamyl ketone and methyl n-propyl ketone (Carpenter, 1949, 1954, and 1957). Of these relatively toxic ketones, 2,4-pentanedione is somewhat exceptional in that it caused no local skin irritation (Smyth, 1941a).

As in oral exposure, delayed death is noted only for trimethylnonanone. At the highest dose tested, 12.9 g/kg, which was lethal to nine of ten exposed rabbits, death was delayed for up to ten days after exposure. While most animals developed erythema, necrosis of the skin was seen only occasionally. Also unlike any of the other ketones on which data are available, trimethylnonanone caused persistent diarrhea (Carpenter, 1948c).

No further details are available on any of the ketones listed in Table 73. As evident from the above discussion, LD_{50} values do not seem to be good indicators of the type of acute toxic response to the dermal application of a given ketone. Consequently, a listing of relative toxicity based on these values does not seem warranted.

c. Acute Inhalation Toxicity

By far the greatest amount of information on the acute toxicity of ketones comes from inhalation studies. As in oral exposures, most of the ketones under review cause narcosis, over a relatively short period of time, which may progress to respiratory arrest during the exposure period. Generally, those animals which survive the exposure period seem to recover rapidly from narcosis and suffer no permanent adverse effects. In a few instances, animals die after the exposure period. These deaths are usually attributed to lung irritation which may include severe congestion and/or hemorrhage.

However, such broad generalizations on acute inhalation toxicity are only of qualitative validity. Although certain basic response patterns are apparent, the specific types of responses may vary markedly in magnitude. For example, some ketones cause rapid and severe irritation to the respiratory tract while others cause only mild irritation even on prolonged exposures. Further, the quantity, quality, and consistency of the information available on the individual ketones varies greatly. Methyl ethyl ketone and cyclohexanone have been extensively studied by a number of investigators who provide detailed data on dose-response relationships, pathology, and mechanisms of action but use differing methods of exposure and criteria of response. At the other extreme, only a rough approximation of the lethal range is available for acetophenone.

Because of the many common features and yet significant diversity found in the available information on the acute inhalation toxicity of ketones, a somewhat different approach will be adopted in the presentation of this data. First, the general methodology used by the various investigators will be compared. Secondly, the common aspects of ketone intoxication will be detailed. This will be followed by capsule summaries of the data available for the individual ketones. Lastly, the relative activities of the various ketones will be discussed within the limitations of the available data.

(i) Methodology

Almost all of the information on the acute inhalation toxicity of ketones comes from three groups of investigators: Smyth and coworkers (references beginning with Smyth, Carpenter, Nycum, and Mellon Institute); Patty and coworkers (Patty _et al._, 1935; Schrenk _et al._, 1936; Yant _et al._, 1936); and Specht and coworkers (1938 and 1940). Most acute inhalation tests have been conducted on either rats or guinea pigs and have involved exposure to a known concentration of ketone vapor over a specified period of time. In the studies by Smyth and coworkers, the vapor concentrations are nominal -- i.e., they are prepared by diluting a known concentrated vapor using a proportioning pump, but the actual vapor concentration to which the animals are exposed is not analytically determined. The other two groups of investigators do analytically determine the levels of ketone vapor in the exposure chambers. Occasionally, Smyth and coworkers also expose animals to "saturated" or "concentrated" vapors generated either by heating the ketone to 170°C (with the consequent possibility of partial oxidation) or by using a fog-nebulizer. In either case, such exposures serve only as rough indications of hazard (Carpenter et al., 1949). Because the concentration of vapor generated will vary widely with the vapor pressure of the ketone and because actual concentrations are not monitored, the results from "saturated" or "concentrated" vapor exposures are not comparable with the results from known concentration exposures.

These three groups of investigators also differ in the type of data presented. Smyth and coworkers attempt to subject animals to exposures that will cause no lethality, fractional lethality, and total lethality by varying either the concentration or the exposure period. Consequently, standard dose-response relationships are often presented. Information on pathology and response patterns from any given exposure, however, is often quite limited. Specht and coworkers (1940) and Patty and coworkers present similar data along with information on time-response and relatively detailed gross pathology.

(ii) General Patterns in Ketone Vapor Intoxication

The primary response to the inhalation of ketone vapors is progressive narcosis. This involves a loss of corneal, auditory, and equilibratory reflexes as well as a general depression of vital signs such as heart rate, respiratory rate, and body temperature. These qualitative similarities were noted by Specht and coworkers (1940) who exposed guinea pigs to the ketones listed below:

*Acetone
Methyl ethyl ketone
*Methyl n-propyl ketone
*Methyl n-butyl ketone
*Methyl n-amyl ketone
Methyl n-hexyl ketone

*Methyl isobutyl ketone
2,5-Hexanedione
*Mesityl oxide
Cyclohexanone

For the compounds marked with an asterisk (*), common pathological findings were also given. The most frequently noted pathological finding is congestion and mild hemorrhage in the lungs. Congestion is also common in the kidneys, spleen, adrenals, and brain, and is attributed to the effects of ketones on the vasomotor center. Selective action by ketones is evident in distention of the renal tubules (Specht et al., 1940).

(iii) Capsule Summaries

METHYL ETHYL KETONE

The acute inhalation toxicity of methyl ethyl ketone is typical of most of the acyclic aliphatic ketones under review. Mortality data from acute exposures to rats, mice, and guinea pigs are summarized in Table 74. Patty and coworkers (1935) noted the following response sequence in guinea pigs exposed to concentrations of 33,000 ppm and 100,000 ppm: irritation of the eyes and nose, lacrimation, incoordination, narcosis, respiratory distress, and death. In addition, opacity of the cornea developed after 30 minutes at the higher concentrations. A similar pattern is detailed by Specht and coworkers (1940) who also noted marked salivation as an initial response to 25,000 ppm. Exposures of 10,000 ppm x 13.5 hours are not fatal to guinea pigs but narcosis is induced after about four hours. At 3,300 ppm, Patty and coworkers (1935) noted neither irritant nor narcotic effects during an exposure period of 13.5 hours. The narcosis induced by exposures to 10,000 - 50,000 ppm over periods of 4-14 hours was accompanied by progressive dose-related decreases in respiratory rate, heart rate, and body temperature (Specht et al., 1940). In non-fatal exposures which caused unconsciousness, narcosis often persisted for several hours after exposure (Patty et al., 1935).

Table 74. Acute Inhalation Toxicity of Methyl Ethyl Ketone

Organism	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats, Female, Sherman, young	6	1000	8	0/6	Mellon Institute, 1945
	6	2000	2	0/6	
	6	2000	4	1/6	
	6	2000	8	5/6	
	6	2000	2	0/6	
	6	4000	2	4/6	
	6	8000	2	6/6	
Rats, Female, Sherman, young	6	4000	8	0/6	Mellon Institute, 1950 [partially summarized in Smyth et al., 1962]
	6	8000	8	3/6	
	6	16000	8	6/6	
Rats, Female, Sherman	[6]	Saturated vapor	0.5	1/6	Mellon Institute, 1949
			1	5/6	
			2	6/6	
Mice	10	8000	4	1/10	Carpenter, 1949
	10	8000	8	6/10	
Guinea Pig	5	8000	8	0/5	Carpenter, 1949
Guinea Pig	6	10000	≈15	no fatality noted	Patty et al., 1935
	6	33000	≈3.3-4.3	fatal	
	6	100000	≈0.75-0.92	fatal	
Guinea Pig, mixed strain, 400-600g	10	25000	3	1/10 (Cumulative deaths)	Specht et al., 1940
		25000	4.5	5/10	
		25000	5.4	7/10	
				10/10 by 48 hrs. after exposure	

Only Patty and coworkers (1935) have described gross pathology in methyl ethyl ketone exposures. In addition to the previously noted corneal opacity at 100,000 ppm, fatally exposed animals had moderate to marked congestion of the lungs, liver, and kidneys, as well as mild congestion of the brain. These findings were also noted in animals that survived narcosis but were sacrificed immediately after exposure. However, these pathological findings were absent in animals that survived narcosis and were sacrificed eight days after exposure (Patty et al., 1935).

Death from acute methyl ethyl ketone inhalation can be attributed to either lung irritation or narcosis. Patty and coworkers (1935) concluded that narcosis was the primary factor because all of the guinea pigs which survived narcosis eventually recovered. However, in comparable exposures, Specht and coworkers (1940) note that some animals survived narcosis and did not die until 24-48 hours after exposure. In these animals, death was probably due to lung congestion.

Little detailed information is available on the rat and mice exposures. In terms of lethal response, both rats and mice are apparently much more susceptible than guinea pigs to methyl ethyl ketone inhalation. This greater tolerance of guinea pigs as opposed to rats holds true for most of the ketones under review. The marked differences in the results from Mellon Institute (1945) and Mellon Institute (1950) have been attributed to variations in the samples of methyl ethyl ketone used in these two tests (Mellon Institute, 1950).

METHYL n-PROPYL KETONE

This ketone seems to be about twice as toxic as methyl ethyl ketone on acute inhalation but has about the same pharmacological effects. A summary of acute inhalation exposures to rats and guinea pigs is given in Table 75 and again demonstrates the greater susceptibility of rats. As with methyl ethyl ketone, acute exposure to guinea pigs caused irritation of the nose and eyes, lacrimation, incoordination, narcosis, respiratory distress, and death. With methyl n-propyl ketone, all of these symptoms were caused at 13,000 ppm x 5 hours and all but death at 5,000 ppm x ≃ 6 hours. None of these effects were produced during a 13.5 hour exposure to 1500 ppm (Yant et al., 1936). Narcosis was accompanied by dose dependent decreases in respiration, heart rate, and body temperature (Specht et al., 1940). In some animals, narcosis persisted for several hours after exposure (Yant et al., 1936).

Table 75. Acute Inhalation Toxicity of Methyl n-Propyl Ketone

Organism	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats, Carworth-Wistar 4-5 weeks, 90-120g	6	2000	4	1/6	Carpenter, 1954 (Smyth et al., 1962)
		4000	4	6/6	
		Saturated vapor [21,000 ppm]**	0.5	0/6	
			1.0	6/6	
Guinea pigs, Female, 400-600g	10	10,000	9	4/10 during exposure, survivors die 48 hrs after exposure	Specht et al., 1940
Guinea pigs	6	5,000	13.5	not fatal	Yant et al., 1936
		13,000	5	fatal	
		50,000	0.8	fatal	

Specht and coworkers (1940) noted congestion and emphysema of the lungs and kidney along with distention of the renal tubules as the primary pathological effects. Also noted was slight congestion of the liver and adrenals, but no changes in the heart, stomach, and pancreas. Congestion was attributed to the vasomotor effect of the ketone. Similar pathology was also noted by Yant and coworkers (1936), who again found that animals subjected to exposures which probably caused initial pathological damage showed no signs of pathology 4-8 days after exposure. Congestion and pinpoint hemorrhage of the lungs were also noted in fatally exposed rats (Carpenter, 1954).

As with methyl ethyl ketone, death during exposure is probably due to narcosis, while death in animals surviving the exposure period is due to lung irritation (Yant et al., 1936; Specht et al., 1940).

DIETHYL KETONE

Few data are available on this ketone. An exposure to 8000 ppm x 4 hours killed four of six Carworth-Wistar rats and exposure to "concentrated" vapors was lethal to some rats after fifteen minutes (Smyth et al., 1954).

METHYL n-BUTYL KETONE

Information on the acute inhalation toxicity of methyl n-butyl ketone gives no indication of its chronic neuropathological effects. As indicated in Table 76, this ketone is about twice as toxic as methyl n-propyl ketone to both guinea pigs and rats. Except for the difference in potency, the pathological response of guinea pigs is identical to that of methyl n-propyl ketone.

Table 76. Acute Inhalation Toxicity of Methyl n-Butyl Ketone

Organism	Number Exposed	Concentration (ppm,v/v)	Duration (hours)	Mortality	Reference
Rats, sex n.s., Carworth-Wistar 90-120g	6	4,000	4	0/6	Smyth *et al.*, 1954
	6	8,000	4	6/6	
	6	Conc. vapor (<5000 ppm)	0.5	0/6	
			>0.5	lethal to some animals	
Guinea pigs, female, mixed strains, 400-600g	10	6,000	6.6	2/10 (cumulative mortality)	Specht *et al.*, 1940
			8.8	7/10 10/10 by 72 hrs after exposure	
	10	12,000	>2 hr.	Lethal	
Guinea pig	6	2,300	13.5	No deaths	Schrenck *et al.*, 1936
		6,500	9.0	Lethal	
		20,000	1.2	Lethal	

METHYL ISOBUTYL KETONE

As indicated in Table 77, this ketone seems to be about twice as toxic to rats as the n-butyl isomer assuming equal sensitivity between the two strains of rats. Although the pathological effects of this ketone are very similar to those of the n-butyl isomer, differences are noted in the narcotic response. While the methyl n-butyl ketone caused decreases in respiratory rate and heart rate, methyl isobutyl ketone caused initial marked depression in these values followed by slight signs of recovery. This indicates that methyl isobutyl ketone has not only a narcotic effect but also a marked irritating effect on the nasal mucosa which caused rapid reflex inhibition of respiration (Specht *et al.*, 1940).

Table 77. Acute Inhalation Toxicity of Methyl Isobutyl Ketone

Organism	Number Exposed	Concentration (ppm,v/v)	Duration (hours)	Mortality	Reference
Rats, sex, n.s., Sherman, 100-150g	6	2,000	4	0/6	Mellon Institute, 1953
		4,000	4	6/6	
		Saturated vapor	0.25	0/6	Smyth *et al*., 1951
			0.5	6/6	
Mice	n.s.	20,000	0.5	Lethal	Shell Chemical Corp., 1957a
Guinea pigs, female	10	1,000	23	No deaths	Specht, 1938
		10,000	4	Lethal to most animals	
		16,300	3.3	9/10 died (1.3-3.3 hours)	
		25,000-30,000	0.75	Lethal to most animals	

METHYL *n*-AMYL KETONE

A summary of the acute inhalation toxicity of this ketone is given in Table 78. This ketone seems to have about the same toxicity to rats as methyl isobutyl ketone. It is, however, markedly more toxic than either of the methyl butyl ketones to guinea pigs in terms of the time required to induce narcosis and death. Its irritant and pathological properties are similar to methyl *n*-butyl ketone (Specht *et al*., 1940).

Table 78. Acute Inhalation Toxicity of Methyl *n*-Amyl Ketone

Organsim	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats, sex, n.s., Carworth-Wistar 4-5 weeks, 90-120g	6	2,000	4	0/6	Mellon Institute, 1958
	6	4,000	4	6/6	
	6	concentrated vapor	0.5	0/6	Smyth *et al*., 1962
			1.0	2/6	
			2.0	5/6	
Guinea pigs, Female, mixed strain, 400-600g	10	2,000	15	No deaths	Specht *et al*., 1940
	10	5,000	2-4.7	Lethal	

METHYL ISOAMYL KETONE

The acute inhalation toxicity of this ketone has been examined only on rats (Carworth Farms-Nelson). Exposures to 1000 ppm x 4 hours caused only poor coordination. Twice this concentration resulted in narcosis after two hours but did not result in any deaths. An exposure to 4000 ppm x 3 hours was lethal to all of the six rats tested. Inhalation of "concentrated" vapor (≈6,000-10,000 ppm) resulted in narcosis in thirty minutes and convulsive breathing during and after the exposure period. Two of the twelve exposed animals died, both of which had capillary breakdown of the lungs (Carpenter, 1957).

ETHYL n-BUTYL KETONE

Sherman rats exposed to 2000 ppm x 4 hours became anesthetized but did not die. Twice this concentration over the same period resulted in the deaths of all six exposed rats (Carpenter, 1948a).

METHYL n-HEXYL KETONE

Because of its very low vapor pressure, Specht and coworkers (1940) exposed guinea pigs only to the highest concentration obtainable, 1300 ppm. This concentration did not prove lethal over a 14 hour exposure period but did cause typical signs of ketone intoxication including coma after twelve hours and progressive decreases in respiratory rate, heart rate, and body temperature. While the latter two parameters showed gradual declines typical of narcotic response, respiration showed an initial sharp decrease characteristic of exposure to irritant vapors. Because of the low concentration which causes coma, Specht and coworkers (1940) have concluded that this ketone has as great, or a greater, depressant effect than other straight chain methyl ketones.

ETHYL sec-AMYL KETONE

Air saturated with this ketone at 25°C (≈3000 ppm) caused irritation of the eyes and respiratory tract of both rats and mice. Three of six mice died as a result of the exposure. Saturated air at 35°C (≈6000 ppm) caused death in all six exposed mice and four of six exposed rats. Both species showed normal signs of ketone intoxication: uncoordination, respiratory distress, and narcosis (Shell Chemical Corporation, 1958).

DIISOBUTYL KETONE

Carpenter and coworkers (1953) have demonstrated both sex and strain differences in the response of rats to this ketone. In exposures to 2000 ppm x 8 hours, seven of twelve female Sherman rats died. However, in identical exposures, male Sherman rats as well as male and female Carworth Farm Wistar rats showed no lethality. Smyth and Carpenter (1941) indicated that guinea pigs are less susceptible to this ketone than rats.

TRIMETHYLNONANONE

"Saturated" vapor (probably less than 700 ppm) of this ketone killed two of six rats in an eight hour exposure causing marked congestion of the lungs (Carpenter, 1948c).

2,4-PENTANEDIONE

Two of six rats exposed to 2000 ppm x 2 hours died within twenty-four hours. Four hours exposure to the same concentration caused death in four of six rats within two hours after exposure. A concentration of 1000 ppm x 1 hour was not fatal but did cause anesthesia and slight irritation of the eyes and nose (Smyth, 1945). Exposures to saturated vapor at 25°C killed no rats in half an hour but caused death in all rats after a one hour exposure. All deaths occurred during anesthesia. Only slight irritation of the lungs was noted (Smyth, 1941a).

2,5-HEXANEDIONE

Because of its low vapor pressure, 2,5-hexanedione has only been tested under "saturated" conditions. Specht and coworkers (1940) were able to generate a concentration of 400 ppm at room temperature. Guinea pigs evidenced only slight transient signs of irritation and a moderate drop in respiratory rate - but no significant changes in heart rate or body temperature - during a 12.5 hour exposure period.

Smyth and Carpenter (1944) found that exposure to "saturated" vapor for one hour caused no deaths in six male Wistar rats. Exposures for greater than one hour caused death in some animals.

DIACETONE ALCOHOL

Like the diones, diacetone alcohol seems to be only a mild irritant. Male Sherman rats exposed to 1500 ppm x 8 hours suffered no lethality and showed only minor signs of irritation to the eyes and nose (Smyth, 1946a).

METHYL ISOPROPENYL KETONE

This unsaturated ketone is clearly the most toxic ketone in acute inhalation exposures. A concentration of 125 ppm x 4 hours was lethal to five of six exposed rats. Saturated vapor killed six exposed rats after a two minute exposure period (Smyth *et al.*, 1951). In non-lethal exposures

(524 ppm x 1.5 hours), this ketone is very irritating to the eyes and nose of rats. Cyanosis and convulsions were noted in rats dying during exposure to 2910 ppm x a few minutes. Animals dying after the exposure period suffered from severe respiratory irritation (Dow Chemical, unpublished data).

MESITYL OXIDE

Summaries of acute inhalation exposures to mesityl oxide with resulting mortalities are given in Table 79. Details on the acute inhalation toxicity of mesityl oxide presented by Specht and coworkers (1940) indicate that this compound is, in some respects, atypical of most other ketones. The response sequence in guinea pigs was characterized by irritation of the mucous membranes, muscular weakness and incoordination, narcosis, cyanosis, and death. As with most other ketones, narcosis was characterized by a steady decline in body temperature, the magnitude of which was proportional to vapor concentration. However, as indicated in Figure 39, the respiratory rate at lower concentrations showed a marked tendency to return to normal. At concentrations of 5,000 ppm (0.5%) and 10,000 ppm (1.0%), the heart rate remained normal or slightly elevated

Table 79. Acute Inhalation Toxicity of Mesityl Oxide

Organism	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats, male, Wistar, 90-120g and	n.s.	500	8	30% mortality during exposure	Smyth *et al.*, 1942
	n.s.	1,000	8	68% mortality	
	20	2,500	8	100% mortality	
Guinea pigs, males and females, 250-300g	n.s.	13,000	0.166	no mortality	
	n.s.		0.25	16% mortality	
	n.s.		0.5	20% mortality	
	n.s.		1.0	100% mortality	
Guinea pigs, female, mixed strains, 400-600g	10	5,000	5.4	3/10 dead, all comatose	Specht *et al.*, 1940
			7.0	6/10 dead 10/10 by 5 hrs after exposure	

during the hour of exposure. This lack of depression indicated some stimulatory pharmacological effect in addition to narcosis. Although pathological findings were similar to methyl n-propyl ketone, the bodies of guinea pigs dying during exposure were described as having a "rather vile smell" not noted with other ketones. The bodies of these animals became rigid prior to death and were found to be distended with gas and fluid in the alimentary canal (Specht *et al*., 1940).

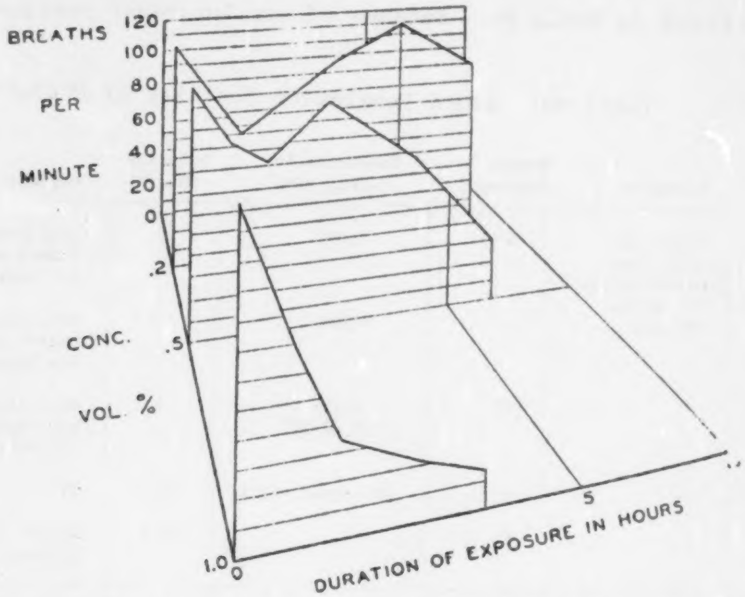


Figure 39. Three-dimensional Graph of Respiratory Rate During Exposures to 0.23, 0.5, and 1.0 per cent Mesityl Oxide Vapor (Specht *et al*., 1940)

No unusual odor was noted by Smyth and coworkers (1942) in exposures to rats and guinea pigs. All deaths occurred during exposure due to narcosis accompanied by moderate lung irritation.

CYCLOHEXANONE

Acute inhalation exposures to cyclohexanone are summarized in Table 80. Because of its low vapor pressure, this ketone was tested only at 4000 ppm by Specht and coworkers (1940). Like most ketones, cyclohexanone caused narcosis and a progressive decrease in body temperature during exposure. Respiratory rate showed a rapid initial decrease characteristic of the reflex effect of irritation to the nasal mucosa. This was followed by a more gradual decline as narcosis progressed. Heart rate, however, initially increased and did not fall below normal until about one hour after exposure. This is somewhat similar to the effect of mesityl oxide at 5000 ppm and indicates that narcosis is not the only marked pharmacological effect of cyclohexanone. Corneal opacity developed in all exposed animals one day after exposure. Specht

Table 80: Acute Inhalation Toxicity of Cyclohexanone

Organism	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats, sex, n.s., Carworth-Wistar 4-5 weeks, 90-120g	6	2,000	4	1/6, anesthesia after 2-5 hours	Nycum *et al.*, 1967
	6	4,000	4	6/6, anesthesia after 1-5 hours	
	[6]	2,639 (2131-3268)	4	LC_{50} for 4 hr. exposure (±1.96 S.D.)	
	6	Saturated vapor	0.5	0/6	
	6		>0.5	death in some animals	
Guinea pigs, female, mixed stock, 400-600g	10	4,000	7.6	3/10 died four hours after exposure	Specht *et al.*, 1940

and coworkers (1940) also noted that recovery from narcosis was unusually slow. Complete recovery, including the reversal of corneal opacity, took several weeks.

The results with rats indicate that, as with most ketones, rats are more susceptible than guinea pigs. Fatally exposed rats had unusually dark red liver, kidneys, and blood (Nycum et al., 1967).

METHYLCYCLOHEXANONE

Rabbits and cats exposed to 2500 ppm x 1 hour experienced respiratory irregularities, poor coordination, and sleepiness but not death. Respiratory irritation, incoordination, and prostration were seen in rats, mice, and guinea pigs exposed to 3,500 ppm x 30 minutes (Flury and Klimmer, 1938).

ISOPHORONE

Smyth (1941b) and Smyth and Seaton (1940) have noted typical signs of ketone poisoning in rats and guinea pigs exposed to 750 ppm - 4600 ppm over several hours. Deaths in both studies were attributed to respiratory paralysis or lung irritation. Rowe and Wolf (1963) have indicated that the samples used in these studies contained significant amounts of impurities more volatile than isophorone. Thus, the summaries of these studies, given in Table 81, may have limited value.

Table 81. Acute Inhalation Toxicity of Isophorone

Organism	Number Exposed	Concentration (ppm, v/v)	Duration (hours)	Mortality	Reference
Rats and Guinea pigs	n.s.	750 ppm	several hours	no death or serious symptoms	Smyth, 1941b
		>750 ppm	several hours	causes death in some animals	
Rats	n.s.	1840	4	caused death in some animals	Smyth and Seaton, 1940
Guinea pigs	n.s.	4600	8	no deaths	

ACETOPHENONE

Exposure to a mist of acetophenone (≈4,400-5,000 ppm) was not lethal to any of six rats over a two hour period but killed six of six after four hours exposure. Death was attributed to anesthesia. Lungs, kidneys, and liver were congested in fatally exposed animals (Smyth, 1946b).

(iv) Comparative Acute Inhalation Toxicity

As should be apparent from the preceding capsule summaries, valid comparisons of acute inhalation toxicity among the ketones are limited by a number of factors. First, the amount and type of information on the different ketones varies greatly. Secondly, the purity of the ketones used in the various studies was not accurately determined. There are indications that unspecified impurities may have affected toxicity estimates on at least two ketones -- methyl ethyl ketone and isophorone. The importance of impurities in other studies cannot be determined. Further, in comparing the studies using rats, the importance of sex and strain differences is also speculative. Definite sex and strain differences seem evident for diisobutyl ketone (Carpenter *et al.*, 1953). Because most ketones seem to act in about the same way, it seems plausible that sex and strain differences may influence the results in studies on other ketones.

Estimates of vapor concentrations which cause varying degrees of response over specified exposure periods have been made for seven of the ketones under review and are summarized in Table 82. These estimates are based on the studies described in the capsule summaries. The values for maximum concentration for several hours without serious disturbance seem to accurately reflect the relative acute inhalation toxicities of these ketones.

Table 82. Acute Effects of Exposure of Guinea Pigs to Various Ketones by Inhalation

Ketone / Single exposures	Single Exposures of Guinea Pigs to Ketonic Solvent Vapors						
	Methyl Ethyl Ketone	Methyl n-propyl Ketone	Methyl n-butyl Ketone	Methyl Isobutyl Ketone	Diisobutyl Ketone	Mesityl Oxide	Isophorone
Kills in a few minutes	---	---	---	---	>2500 ppm	13000 ppm	>4600 ppm
Dangerous to life in 30 to 60 minutes	50000 to 100000 ppm	30000 to 50000 ppm	10000 to 20000 ppm	24000 to 28000 ppm	>2500 ppm	5000 ppm	>4600 ppm
Dangerous to life in several hours	---	8000 to 10000 ppm	4000 to 6000 ppm	5000 50 9000 ppm	---	---	---
Maximum concentration for 60 minutes without serious disturbance	10000 ppm	5000 ppm	3000 ppm	9000 ppm	>2500 ppm	1000 ppm	>4600 ppm
Maximum concentration for several hours without serious disturbance	3000 ppm	2000 to 4000 ppm	1500 ppm	4000 ppm	1000 ppm	200 ppm	880 ppm
Maximum concentration for several hours with slight or no symptoms	---	1500 ppm	1000 ppm	2500 ppm	750 ppm	100 ppm	750 ppm
References	Carpenter *et al.*, 1953	Smyth & Seaton, 1940	Smyth *et al.*, 1942	Schrenk *et al.*, 1936	Patty *et al.*, 1935	Specht, 1938	Yant *et al.*, 1936

Mesityl oxide is the most toxic of this group. With the exception of the other acyclic unsaturated ketone, methyl isopropenyl ketone, mesityl oxide is the most toxic ketone under review.

The straight chain methyl ketones seem to increase in acute inhalation toxicity with increasing molecular weight. This pattern has been noted by Specht and coworkers (1940), who showed a positive relationship between oil over water partition coefficients and the narcotic effectiveness for these ketones as indicated in Table 83. The value of C is defined as the concentration of vapor necessary to induce coma over a standard time interval relative to acetone where 1/C equals one. These values are based on the previously discussed study of the effect of several ketones in guinea pigs. Similar patterns are not apparent for the branched chain or cyclic ketones.

Because the information in this section is relatively diffuse, Table 84 is presented summarizing the oral, dermal, and inhalation exposures to the ketonic solvents.

Table 83. Narcotic Effectiveness Compared to Oil Over Water Partition Coefficients for Various Ketones (modified from Specht *et al.*, 1940)

Ketone	Narcotic effectiveness	Partition coefficients, oil over water				
	(Relative) to Acetone 1/C	Olive oil	Cottonseed oil	Lard oil	Cedarwood oil	L. Mineral oil
Acetone	1.0	0.11	0.16	0.16	0.12	0.03
Methyl ethyl	3.9	1.87	1.70	2.39	2.19	0.82
Methyl propyl	4.2	16.58	9.04	7.66	11.55	11.30
Methyl *n*-butyl	9.8	26.52	18.32	8.95	30.18	15.72
Methyl *n*-amyl	11.8	42.16	26.90	18.29	30.18	49.20
Methyl *n*-hexyl	19.5	59.00	30.50	17.00	30.18	40.80
Methyl isobutyl	5.28	20.640	24.000	---	---	26.900
Methyl isobutenyl	8.29	4.550	4.670	---	---	3.060
2,5-Hexanedione	3.87	0.056	0.050	---	---	0.025
Cyclohexanone	4.15	24.090	10.410	---	---	7.660

Table 84. Summary of Acute Oral, Dermal, and Inhalation Toxicity Data of Various Ketonic Solvents

Compound	Oral LD_{50} Rats (mg/kg)	Dermal LD_{50} Male rabbits (g/kg)	Inhalation Exposures ppm x duration in hrs. (lethality data in parenthesis)	
			Rats	Guinea Pig
Simple Saturated Ketones				
4 carbons				
Methyl ethyl ketone	3.98 (3.94-4.01) [M] 5.53 (4.50-6.82) [F]	8.1	8000 x 8, (3/6)	33,000 x 3.8 (lethal)
5 carbons				
Methyl n-propyl ketone	3.73(2.68-5.21) [M]	6.5(2.9-14.4)	2000 x 4 (1/16)	10,000 x 9 (4/10)
Diethyl ketone	2.14(1.54-2.29) [M]	16.2	8000 x 4 (4/6)	n.d.a.
6 carbons				
Methyl n-butyl ketone	2.59(2.11-3.18) [M]	4.85(3.44-6.80)	8000 x 4 (6/6)	6,000 x 6.6 (2/10) 12,000 x 2 (lethal)
Methyl isobutyl ketone	4.57 [M] 2.08(1.91-2.27) [F]	16.0 not lethal	4000 x 4 (6/6)	10,000 x 4 (lethal)
7 carbons				
Methyl n-amyl ketone	1.67(1.48-1.88) [F]	10.3(7.6-13.9)	4000 x 4 (6/6)	5,000 x 3.3. (lethal)
Methyl isoamyl ketone	3.48(2.12-5.66) [M]	8.8(6.0-13.1)	4000 x 3 (6/6)	n.d.a.
Ethyl butyl ketone	2.76(2.56-2.98) [M]	16.3 not lethal	4000 x 4 (6/6)	n.d.a.
8 carbons				
Methyl n-hexyl ketone	n.d.a.	n.d.a.	n.d.a.	1300 x 12 [F] not lethal
Ethyl n-amyl ketone	>5[n.s.] not lethal	>5 not lethal	n.d.a.	n.d.a.
	3.5	n.d.a.	6000 x 8 (4/6)	n.d.a.
9 carbons				
Diisobutyl ketone	5.75(4.69-7.06) [M]	16.2	2500 x 4 (3/6)	2,500 x 8 (2/4)
12 carbons				
Isobutyl heptyl ketone	8.74(7.18-9.99) [M]	9.0(7.7-10.6)	<700 x 8 (2/6)	n.d.a.
Other Saturated				
5 carbons				
2,4-Pentanedione	0.97(0.90-1.05) [M]	4.85	2000 x 2 (2/6) 2000 x 4 (4/6)	n.d.a.
6 carbons				
2,5-Hexanedione	2.7	6.4	1700 x >1 (lethal)	400 x 12.5 not lethal
Diacetone alcohol	4.0	13.6(12.8-14.6)	1500 x 8 not lethal	n.d.a.
Unsaturated				
5 carbons				
Methylisopropenyl ketone	0.18[n.s.]	0.2(0.06-0.66)	125 x 4 (5/6)	n.d.a.
6 carbons				
Mesityl oxide	1.12(0.99-1.28) [M]	5.13(3.66-7.21)	500 x 8 (30%)	5000 x 5.4 (3/10)
Alicyclic and Aliphatic				
6 carbons Cyclohexanone ketone	1.54(1.14-2.08) [M]	0.948(0.596-1.54)+ 10.2-23+	2000 x 4 (1/16)	4000 x 7.6 (3/10)
7 carbons Methylcyclohexanone ketone	1.0-1.25**	4.9-7.2	3500 x 0.5 not lethal	3500 x 0.5 prostration but not lethal
9 carbons Isophorone ketone	2.12[F]	1.39	1840 x 4 (lethal)	4600 x 8 not lethal
8 carbons Acetophenone ketone	0.90(0.81-1.00) [M] 2.22(1.59-3.10) [M] 2.55[F]	3.08+ 16.3 (11.1-24.2)+	n.d.a. n.d.a.	n.d.a.

Key: ** - rabbits

+ - see text for discussion of conflicting data

n.s. - not specified

n.d.a. - no data available

d. Acute Parenteral Toxicity

The acute toxicity of the ketonic solvents on parenteral administration has received relatively little attention. Table 85 summarizes most of the available information. While most of these studies use intraperitoneal injections, the rather disparate results for mesityl oxide and acetophenone would seem to indicate that these studies are not readily comparable to one another. However, studies by a single group of investigators on a related series of ketones may give reliable indications of relative toxicity. Of the studies in Table 85, this would include the work of Haggard and coworkers (1945) on the amyl ketones, as well as the studies by Caujolle and coworkers (Caujolle and Roux, 1954; Caujolle *et al.*, 1953) on cyclohexanone and its methyl analogues.

Table 85. Acute Toxicity of Ketones by Injection

Chemical	Route	Organism	Dose (g/kg)	Mortality	Reference
Methyl ethyl ketone	intraperitoneal	guinea pig	2.0	lethal to 1 of 4 animals	DiVincenzo and Krasavage, 1974
Methyl *n*-propyl ketone	intraperitoneal	rat	2.53	lethal dose (see text)	Haggard *et al.*, 1945
Methyl isopropyl ketone	intraperitoneal	rat	2.98	lethal dose (see text)	Haggard *et al.*, 1945
Diethyl ketone	intraperitoneal	rat	2.79	lethal dose (see text)	Haggard *et al.*, 1945
Methyl *n*-butyl ketone	intraperitoneal	rat	0.914	LD_{10}	Raleigh, 1974
Methyl isobutyl ketone	intraperitoneal	guinea pig	1.0	lethal to 1 of 4 animals	DiVincenzo and Krasavage, 1974
Ethyl *sec*-amyl ketone	intraperitoneal	mice	0.406	LD_{50}	Shell Chemical Corporation, 1958
Diacetone alcohol	intravenous	rabbit	3.25	lethal dose	Flury and Klimmer, 1938
Mesityl oxide	intraperitoneal	mouse	0.354	LD_{50}	Shell Chemical Corporation, no date
Cyclohexanone	intravenous	dog	0.63	lethal dose	Caujolle and Roux, 1954
2-Methylcyclohexanone	intravenous	dog	0.27	lethal dose	Caujolle *et al.*, 1953
3-Methylcyclohexanone	"	"	0.31	" "	" "
4-Methylcyclohexanone	"	"	0.37	" "	" "
Acetophenone	intraperitoneal	mice	1.07	LD_{50}	Quevauviller, 1946
	intraperitoneal	mice	0.1-0.2	approx. LD_{50}	Doull *et al.*, 1962

In the study by Haggard and coworkers (1945), rats were given repeated intraperitoneal injections of three amyl ketones - methyl *n*-propyl ketone, methyl isopropyl ketone, and diethyl ketone. These injections were given in decreasing amounts until respiratory failure occurred, at which time ketone venous blood levels were determined. This type of repeated dosing was used in an attempt to achieve equilibrium between blood and tissue ketone levels at the time of death. Assuming a coefficient of distribution between blood and tissue of 0.8, the concentration of ketone present in the animal's body which would cause death by respiratory failure could then be calculated. This value was termed the "basic lethal amount." The basic lethal amounts and venous blood levels at respiratory failure for the three amyl ketones are given in Table 86.

Table 86. Comparative Toxicities of Amyl Ketones Administered Intraperitoneally to Rats (Haggard *et al.*, 1945)

Ketone	Amount Administered (g/kg)	Concentration in Venous Blood at Respiratory Failure (mg/100 ml)	Basic Lethal Amount (g/kg)
Methyl *n*-propyl	2.53	156	1.25
Diethyl	2.79	155	1.25
Methyl isopropyl	2.98	127	1.02

The presumed advantage of using the basic lethal amount rather than the amount administered as an index of toxicity is that the basic lethal amount should be consistent for any given chemical, regardless of the route of administration, providing that blood/tissue equilibrium is reached. Using this criterion, methyl isopropyl ketone would be considered the most, rather than the least, toxic of the amyl ketones, while methyl n-propyl ketone and diethyl ketone would be equitoxic. Because blood levels are not available in any of the other studies on ketone toxicity and because Haggard and coworkers (1945) did not use other routes of administration, the validity of this system for comparing ketone toxicity cannot be evaluated.

The work of Caujolle and coworkers (Caujolle and Roux, (1954; Caujolle et al., 1953), summarized in Table 85, clearly indicates that the methylcyclohexanones are about twice as toxic as cyclohexanone on intravenous injection to dogs. While toxicity tests by other routes of administration do not use individual methylcyclohexanone isomers, these results are in agreement with the relative dermal - but not oral - toxicity of cyclohexanone and methylcyclohexanone noted by Treon and coworkers (1943a).

Two studies, not summarized in Table 85, have noted strikingly similar hyperbolic relationships between toxicity and molecular weight for two different groups of ketones on parenteral administration. Caujolle and Caujolle (1965) determined the toxicity of a series of alicyclic ketones from four to fifteen carbons by intraperitoneal injections to mice and rats. The results with both species were similar. In assessing toxicity by a variety of criteria - including minimum lethal dose, 24 hour LD_{50} and LD_{100}, as well as maximum non-lethal dose - the toxicity consistently increased going from four to eight carbons and decreased going from eight to fifteen carbons. Jeppsson (1975) found a nearly identical pattern for the toxicity of a series of acyclic aliphatic ketones on intravenous injection to mice using AD_{100} (anesthetic dose) as well as LD_{50} and LD_{100} as indices of toxicity. These results are summarized in Table 87.

Table 87. Anesthetic (AD100) and Toxic Doses (LD50 and LD100) of Some Ketones After Intravenous Administration to Mice. LD50 was Estimated in 60 Animals/Compound and AD100 and LD100 in About 10 Animals/Compound. Confidence Limits are Given at P = 0.05 (Jeppsson, 1975)

Ketones	AD100 mol x 10^{-3}/kg	LD50 mol x 10^{-3}/kg	LD100 mol x 10^{-3}/kg
3-Pentanone	4.54 (3.92-5.17)	5.97 (5.47-6.47)	13.34 (12.03-14.65)
4-Heptanone	1.32 (1.16-1.47)		2.37 (2.11-2.63)
5-Nonanone	0.83 (0.70-0.96)	0.97 (0.93-1.05)	1.83 (1.64-2.02)
6-Undecanone	1.19 (1.02-1.37)	0.69 (0.64-0.73)	2.13 (1.92-2.35)
7-Tridecanone	9.51 (7.45-11.56)		17.70 (10.52-24.89)
8-Pentadecanone	13.40 (10.56-16.25)	5.29 (5.03-5.56)	50.31 (48.64-51.97)
9-Heptadecanone	28.52 (26.26-30.78)		39.46 (36.57-42.35)

The similarity between the patterns noted by Jeppsson (1975) and Caujolle and Caujolle (1965) is illustrated in Figure 40, which compares the LD_{100} value to the number of carbons for each series of ketones.

This pattern is not unlike that suggested in Figure 38 (p. 213) for the oral toxicity of acyclic aliphatic ketones. Jeppsson (1975) has explained this parabolic relationship between the number of carbons and toxicity both in terms of lipophilicity and increasing molecular size. Given a homologous series of compounds, the oil/water partition coefficient will increase with the addition of methylene groups. Thus, starting with the lowest molecular weight compound, toxicity will initially increase with molecular weight, because of increased ability to reach and interact with lipid receptor sites.

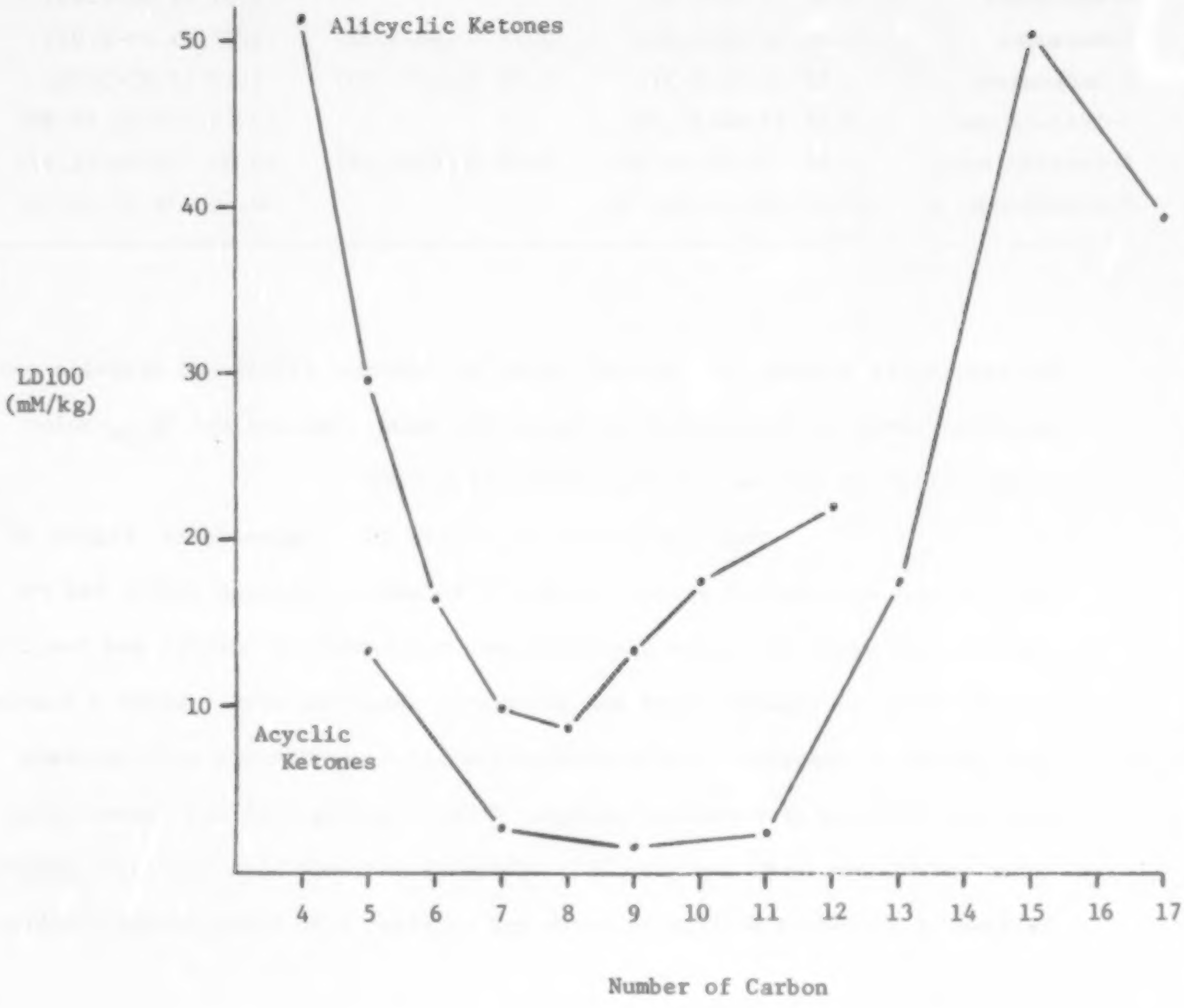


Figure 40. Relationship Between Molecular Weight and LD_{100}'s For a Series of Alicyclic Ketones (Caujolle and Caujolle, 1965) and Acyclic Ketones (Jeppsson, 1975)

However, increased lipophilicity past an optimum point will result in the rapid sequestering of the compound in fat tissue, preventing interaction with receptor sites. Further, increasing molecular size will eventually counteract, increasing lipophilicity and resulting in slower passage through lipid membranes.

Serum ornithine carbamyl transferase (OCT) has been used as an index of the hepatotoxic effects of acetone, methyl ethyl ketone, and methyl isobutyl ketone on intraperitoneal injection to male guinea pigs (DiVincenzo and Krasavage, 1974). Because most of this enzyme is present in the liver, increased enzyme activity in the serum is indicative of liver cell rupture. The effects of these ketones on OCT serum is presented in Table 88. Lethality was noted only at the highest doses of methyl ethyl ketone and methyl isobutyl ketone (see Table 85, p. 240).

Table 88. Effects of Acetone, Methyl Ethyl Ketone, and Methyl Isobutyl Ketone on Serum Ornithine Carbamyl Transferase in Guinea Pigs (DiVincenzo and Krasavage, 1974)

Ketone	Dose (g/kg)	Mean OCT Activity (Range) in International Units of Enzyme Activity
Control	---	2.02(0-8.9)
Acetone	1.5	1.1
	3.0	2.3
Methyl ethyl ketone	0.75	1.5
	1.5	4.5
	2.0	10.8
Methyl isobutyl ketone	0.5	4.0
	1.0	6.4

Acetone and methyl isobutyl ketone caused neither changes in OCT levels nor liver damage at the levels tested. Methyl ethyl ketone, however, resulted in slightly elevated OCT levels at 2.0 g/kg and obvious lipid deposition in the liver at 1.5 g/kg and 2.0 g/kg, but actual tissue damage was not noted at any dose level. This is consistent with the results from other exposure routes indicating that the liver is not a primary target in ketone intoxication.

e. Primary Skin Irritation

Primary skin irritation caused by the ketones has been evaluated by the uncovered application of the chemical to the clipped intact skin of a rabbit's belly. Either undiluted solvents or dilutions of 10, 1, 0.1, and 0.01 percent in 0.01 ml are applied to five rabbit bellies and the skin response is graded 24 hours after application. The ten-point grading system used by Smyth and Carpenter in their Range Finding lists (1944, 1948a, b, c, 1949, 1954, 1957, 1962) as first presented in 1944 is based on the degree of capillary injection, erythema, and edema and/or necrosis of the skin which occurs in 24 hours (see Table 89).

Table 89. Grading System for Primary Skin Irritation
(After Smyth *et al.*, 1949)

Grade	Reaction
1	None from undiluted material.
2	Trace of capillary injection from undiluted material.
3	Strong capillary injection from undiluted material.
4	Slight erythema from undiluted material.
5	Strong erythema from undiluted material.
6	Necrosis from undiluted material; 10 percent solution causes reaction no more severe than edema.
7	One percent solution causes no more severe reaction than edema.
8	0.1 percent solution causes no more severe reaction than edema.
9	0.01 percent solution causes no more severe reaction than edema.
10	Dilution smaller than a 0.01 percent solution.

The ketonic solvents as a group are not severe skin irritants when applied uncovered to the clipped belly of rabbits. Test results are presented in Table 90 below. The volatile nature of the solvents leads to fairly rapid evaporation and in several cases - i.e., methyl n-propyl ketone, methyl n-butyl ketone, methyl isoamyl ketone, diacetone alcohol, and cyclohexanone - no skin irritation was found after the 24 hour test period. In no case did edema or necrosis occur.

Table 90. Primary Skin Irritation of Ketonic Solvents in Rabbits

Ketone	Nature of Irritation	Reference
Methyl ethyl ketone	Trace of capillary injection in two of five animals tested	Carpenter, 1949
Methyl n-propyl ketone	No irritation; solvent evaporates too quickly	Carpenter, 1954
Diethyl ketone	Trace of capillary injection from undiluted solvent	Smyth et al., 1954
Methyl n-butyl ketone	No irritation from undiluted solvent	Smyth et al., 1951
Methyl isobutyl ketone	Trace of irritation	Union Carbide, 1968
Methyl n-amyl ketone	Slight erythema from undiluted material	Mellon Institute, 1958
Methyl isoamyl ketone	No irritation from undiluted solvent	Carpenter, 1957 Smyth et al., 1962
Ethyl n-butyl ketone	Trace of capillary injection in two of five animals	Carpenter, 1948a Smyth et al., 1949
Diisobutyl ketone	Erythema in one of five and marked capillary injection in two of five animals tested	Carpenter, 1948b
Isobutyl heptyl ketone	Erythema in two of five and minimal capillary injury in three of five	Carpenter, 1948c
Other Saturated		
2,4-pentanedione	Trace irritation, erythema	Mellon Institute, 1955a
Diacetone alcohol	No irritation from undiluted solvent	Mellon Institute, 1955b
Unsaturated		
Mesityl oxide	Slight capillary injection	Mellon Institute, 1952
Alicyclic and Aliphatic		
Cyclohexanone	No irritation from the undiluted solvent	Nycum et al., 1967
Isophorone	Mild irritation with slight erythema	Truhaut et al., 1972
Acetophenone	Slight erythema from undiluted solvent	Mellon Institute, 1956

f. Eye Irritation

Carpenter and Smyth (1946) have studied the severity of chemical burns of the eyes caused by application of various solvents including some ketones. The test utilized normal albino rabbits. Undiluted single instillations of varying amounts (0.005, 0.02, 0.10 and 0.5 ml) or dilutions of 5, 10, 15 and 40 percent in 0.5 ml quantities were directly applied into the conjunctival sac of both eyes and allowed one minute of direct contact before the eyelids were released. The eye injury was assessed 18 to 24 hours after administration in both eyes, one of which was stained with fluorescein. The system of scoring the injury and the grading of the injury are given in Table 91A and B.

Table 91. (A) System For Numerical Scoring of Injury to the Rabbit Eye 24 Hours After Application of a Material (B) Grades of Injury Employed For Rating the Relative Damage Produced By Chemicals in the Eye

(Carpenter and Smyth, 1946)

A

Injury Grade	Definition
1	0.5 ml undiluted gives injury of 0 to 1.0 points
2	0.5 ml undiluted gives injury of over 1.0 up to 5.0 points
3	0.1 ml undiluted gives injury of up to 5.0 points (0.5 ml gives over 5.0)
4	0.02 ml undiluted gives injury of up to 5.0 points (0.1 ml gives over 5.0)
5	0.005 ml undiluted gives injury of up to 5.0 points (0.02 ml gives over 5.0)
6	Excess of 40 percent solution gives injury of up to 5.0 points (0.005 ml gives over 5.0)
7	Excess of 15 points solution gives injury of up to 5.0 points (40 percent gives over 5.0)
8	Excess of 5 percent solution gives injury of up to 5.0 points (15 percent gives over 5.0)
9	Excess of 1 percent solution gives injury of up to 5.0 points (5 percent gives over 5.0)
10	Excess of 1 percent solution gives injury of over 5.0 points.

B

	Points	Maximum
Symptom Visible Before Flourescein Staining		
Cornea dull	2	
Cornea opaque, less than half of area	4	
Cornea opaque, more than half of area	6	6
Keratoconus		6
Iritis, slight internal congestion	1	
Iritis, marked internal congestion	2	2
Symptom Visible After Flourescein Staining		
(If necrosis is diffuse assign points corresponding to half observed area.)		
Necrosis on less than 5 percent of cornea	1	
Necrosis on 5 to 12 percent	2	
Necrosis on 13 to 37 percent	3	
Necrosis on 38 to 62 percent	4	
Necrosis on 63 to 87 percent	5	
Necrosis on 88 to 100 percent	6	6
Total		20

The results of the rabbit eye irritation tests have been reported in the Range Finding lists by Smyth and coworkers (1946, 1948, 1949, 1954, 1962, 1969). These data are compiled in Table 92 .

The majority of ketonic solvents cause from a trace to a moderate degree of eye injury according to the Carpenter and Smyth (1946) guidelines. Truhaut and coworkers (1972) have modified this scoring system and report effects on individual portions of the eye; these workers found isophorone to be a moderate irritant to the mucous membrane of the eye by producing conjunctivitis as well as causing some corneal opacity which was curable. These results concur with the moderate rating given by Carpenter and Smyth (1946) (see Table 92).

Only one ketone tested caused a more severe injury, a grade eight injury. Application of a 15 percent solution of acetophenone to the rabbit's eye gives a score of over 5.0 points on the 20 point scale in Table 91.

Table 92. Rabbit Eye Irritation from Ketones

Ketone	Degree of Eye Injury[1]	Grade of Eye Injury	References
Simple Saturated Aliphatics			
Methyl n-propyl ketone	Minor	Grade 3	Smyth et al., 1962
Diethyl ketone		Grade 4	Smyth et al., 1954
Methyl n-butyl ketone		Grade 3	Smyth et al., 1954
Methyl isobutyl ketone	Minor	Grade 4	Mellon Institute, 1953
Methyl n-amyl ketone	Trace	Grade 2	Smyth et al., 1962
Methyl isoamyl ketone	Trace	Grade 2	Smyth et al., 1962
Ethyl n-butyl ketone	Minor	Grade 3	Smyth et al., 1949
Diisobutyl ketone	Trace	Grade 1	Carpenter and Smyth, 1946
Isobutyl heptyl ketone	Trace	Grade 1	Smyth et al., 1949
Other Saturated			
2,4-pentanedione	Minor	Grade 3	Mellon Institute, 1955
2,5-hexanedione		Grade 4	Carpenter and Smyth, 1946
Diacetone alcohol	Moderate	Grade 4	Mellon Institute, 1955b
Unsaturated			
Mesityl oxide	Moderate	Grade 5	Carpenter and Smyth, 1946
Alicylic and Aliphatic			
Cyclohexanone	Moderate	Grade 5	Carpenter and Smyth, 1946 Smyth et al., 1969a
Isophorone	Moderate	Grade 5	Carpenter and Smyth, 1946
Acetophenone	Severe	Grade 8	Carpenter and Smyth, 1946

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[1] Union Carbide, 1968

2. Subacute and Chronic Toxicity

a. Subacute and Chronic Oral Toxicity

Subacute or chronic oral toxicity data are available on only four of the ketones under review. This information is summarized in Table 93. None of the exposures described in this table proved fatal to any of the animals tested. Some kidney damage is evident in exposures to diacetone alcohol, methyl n-amyl ketone, and acetophenone. This is consistent with the observation made by Specht and coworkers (1940) in acute inhalation exposures - i.e., ketones may have a selective action on the kidneys. However, not too much can be made of this observation because, in most cases, damage is indicated only by a slight rise in kidney weight relative to total body weight. The studies of Hagan and coworkers (1967), Smyth (1946b), and Novogorodova and coworkers (1967) apparently involved rather detailed pathological investigations. None of these studies report pathological changes in the kidneys.

Novogorodova and coworkers (1967) did note apparent liver damage and adverse central nervous system effects in rats attributable to cyclohexanone exposure over a six month period. Male rats exposed to several concentrations - 0.01 mg/kg, 0.05 mg/kg, and 5 mg/kg - were tested for reflex activities in response to light stimuli. The 0.05 mg/kg/day group demonstrated a retarded response reinforcement, an increased latency period in response to light, and an increased number of conditioned response failures. In the 5 mg/kg/day dosage group, these changes were aggravated to the point where 3 of the 5 rats in the group stopped functioning within 2 weeks. Their

Table 93. Subacute and Chronic Oral Toxicity of Ketones

Chemical	Animal	Mode of Administration	Dose (mg/kg/day)	Duration (days)	Mortality	Details	Reference
SATURATED ALIPHATICS							
Diacetone alcohol	Rats, 10 at each dose level	in drinking water	10	30	no deaths	"no effect"	Mellon Institute, 1955b (similar data reported in Smyth and Carpenter, 1948)
			40	30	no deaths	cloudy swelling of kidney tubules in one rat	
Methyl n-amyl ketone	Rats, CFE strain 5 female (85-95g) & 5 male (95-115g) per dose level	intubation, in oil	100	14	no deaths	increase in liver weight relative to total body weight at both dose levels in males only	Gaunt et al., 1972
			500	14	no deaths		
	same as above	as above	100	72	no deaths	increase in liver weight in males noted only at higher dose along with increased number of cells excreted in urine	
			500	72	no deaths		
	same as above except 15 of each sex used per dose level	as above	20	91	no deaths	no effects noted	
			100	91	no deaths	increase in relative kidney weight in males increase number of cells excreted in urine in both males and females	
			200	91	no deaths	increased relative liver weights in males and females, increased kidney weights in males increased number of cells excreted in urine in both males and females	
Cyclohexanone	Rats, male,	intubation	0.01	180	no deaths	no effect noted	Novogorodova et al., 1967
			0.05	180	no deaths	slight changes in conditioned reflex activity	
			5.0	180	no deaths	marked changes in conditioned reflex activity degenerative morphological changes of nervous system, liver, stomach, and spleen [see text for details]	
	Mice	intubation	280	25	no deaths	no changes in weight gain and general condition decline in work capacity on 25th day	
Acetophenone	Rats, 5 male and 5 female per exposure group	in diet	1, 6, & 25	30	no deaths	questionable increase in liver and kidney weights definite increased liver weight relative to total body weight - questionable increase in kidney weight [see text for details]	Smyth, 1946b
	Rats, Weaning Osborne-Mendel 10 male and 10 female	in diet	1000	119	no deaths	no effect	Hagan et al., 1967

autopsies reveal degenerative liver changes, hyperemia of the mucous membranes of the stomach and plethora in the spleen. Liver function tests were performed on 4 rats who received 0.05 mg/kg cyclohexanone for six months and the only change noted was a stable reduction in serum albumin, a parameter which is often effected in liver disease (Novogorodova _et_ _al_., 1967).

Cyclohexanone at levels of 1% in the diet has also been shown to slightly inhibit weight gain in first generation male and female mice over exposure periods of 110 days. However, second generation mice show no growth retardation (Gondry, 1973).

b. Subacute and Chronic Inhalation Toxicity

Chronic inhalation exposures to various ketones which do not induce peripheral neuropathy are summarized in Table 94. It will be noted that adverse effects, when induced, are qualitatively similar to acute inhalation exposures.

Methyl isobutyl ketone, while not showing any unequivocal peripheral neuropathic activity, did cause narcosis in rats during multiple six hour exposure periods to 1500 ppm. In addition, kidney damage was indicated in rats by increased organ weights, toxic nephrosis of the proximal tubules, and progressive hyaline droplet degeneration (MacEwen _et_ _al_., 1971; MacKenzie _et_ _al_., 1971; and Vernot _et_ _al_., 1971).

Carpenter and coworkers (1953) also noted statistically significant increases in kidney weights in male and female rats in multiple exposures to diisobutyl ketone at concentrations of 250 ppm and above. As in acute exposures, female Sherman rats were much more susceptible in repeated exposures to high concentrations (1650 ppm) of this ketone. Further, the increased liver and kidney weights in female, but not male, rats at 250 ppm indicate that this increased susceptibility also occurs in chronic exposures (Carpenter _et_ _al_., 1953).

The unsaturated aliphatic ketones, methyl isopropenyl ketone and mesityl oxide, also show signs of kidney damage over prolonged exposures. As might be expected from acute inhalation studies, methyl isopropenyl ketone is the more toxic and rats are more susceptible than guinea pigs. In subacute exposures (30 ppm x 7 hrs/day x 20 exposures), lung irritation and leucocytosis

Table 94. Subacute and Chronic Inhalation Toxicity of Various Ketones

Chemical	Animal	Conc. (ppm, v/v)	Hr/Day	Duration in Days	Mortality	Details	Reference
SATURATED ALIPHATICS							
Methyl ethyl ketone	Guinea pigs, 15 Rats, 25	235 ± 26	7	84 (60 exposures, 5 day/wk x 12 wk)	no deaths attributed to exposure	No significant difference from controls in growth, hematological or pathological examinations	La Belle and Brieger, 1955
	Rats, Sherman, 15 male & 15 female per dose level Guinea pigs, mixed-strain, 10 male per dose level	125, 250, 500, and 1000	n.s.	30	no deaths	No significant histopathological changes in lung, liver, or kidney No statistically significant deviation from controls in body, liver, or kidney weights	Mellon Institute, 1950
Methyl isobutyl ketone	Mice, 14	20,000	0.33	11	10/14 died. Deaths occurred after exposure periods 1-6, 10 (one death each) and period 9 (three deaths)	[This is not dissimilar to acute lethal data. This is really repeated acute exposures.]	Shell Chemical, 1957a
	Rats, young adult, 6	1,500 (contaminated with 0.5% MBK)	6	<100 [5day/week for up to 5 months]	no deaths	Slight narcosis during exposure Normal weight gain No signs of neurological disfunction Minimal but consistent distal axonal changes without actual nerve fiber degeneration	Spencer et al., 1975 Spencer, 1975
	Mice, ICR, 40 Dogs, beagles, 8 Monkeys, rhesus, 4	100	24	14	no deaths	No signs of toxic response at either dose level	MacEwen et al., 1971 Vernot et al., 1971 MacKenzie, 1971
		200	24	14	no deaths		
	Rats, Wistar, 50	100	24	14	no deaths	Increased kidney weights	
		200	24	14	no deaths	Increased kidney and liver weights, toxic nephrosis in proximal tubules of kidney	
	Monkeys, rhesus, 2	100 (260 torr)	24	90	no deaths	No significant variation from controls	
	Dogs, beagles, 8	atmosphere of 68% O_2 and 32% N_2					
	Rats, Wistar, 80	as above	24	90	no deaths	No effect on total body weight gain Increased liver and kidney weights Kidney pathology: progressive hyaline droplet degeneration, reversible No liver pathology	
Diisobutyl ketone	Rats, Sherman, 15 of each sex per exposure level	125	7	42 (30 exposures, 5days/wk x 6 weeks)	no deaths	No effects noted	Carpenter et al., 1953
		250	"	"	no deaths	Increased liver and kidney weights in females Decreased liver weights in males	
		500	"	"	no deaths	Increased liver and kidney weights in males and females	
		920	"	"	no deaths	" "	
		1650	"	"	all 15 females and 2 of 15 males died during 1st exposure	During 1st and 2nd exposure only, males exhibited incoordination. Surviving males had increased liver and kidney weights	
	Guinea pigs, mixed strain, males, 10	125	"	"	no deaths	No effects noted	
		250	"	"	no deaths	Lower liver weights	

Table 94. (cont'd)

Chemical	Animal	Conc. (ppm, v/v)	Hr/ Day	Duration in Days	Mortality	Details	Reference
UNSATURATED ALIPHATICS							
Methyl isopropenyl ketone	Rat	15	7	up to 140 (up to 100 exposures)	slight increase	Leucocytosis Slight kidney injury involving minor increase in weight and tubular injury Irritation of nose and eyes	Dow Chemical, unpublished data
	Guinea pigs and rabbits	"	"	" "	no increase	Irritation of nose and eyes	
	Rats	30	7	28 (20 exposures)	some increase	Distinct leucocytosis Lungs severely affected Some changes in kidney and spleen Weight loss Irritation of nose and eyes	
	Guinea pigs	"	"	"	no increase	Depressed growth Irritation of nose and eyes	
	Rabbits	"	"	"	no increase	Irritation of nose and eyes	
Mesityl oxide	Rats, Male, Wistar, 90-120 g, 10 animals per exposure group	50	8	42 (30 exposures)	no deaths	See text	Smyth et al., 1942, and Smyth, 1941c
		100	"	" "	" "		
		250	"	" "	" "		
		500	"	14 (10 exposures)	9/10 died due to exposure		
	Guinea pigs, both sexes, 250-300 g, 10 animals per exposure group	50	8	(42 exposures)	no deaths		
		100	"	" "	no deaths		
		250	"	" "	no deaths		
		500	"	14 (10 exposures)	2/10 died due to exposure		
	Rats	300	2	30	no deaths	Leucocytosis and hypertrophy of liver, kidney, and spleen	Ito, 1969
	Rabbits	25	4	189	no deaths	Anemia and Leukopenia	
CYCLIC AROMATICS and ALIPHATICS							
Cyclohexanone	Rabbits, young, 4 per exposure group	190	6	70 (50 exposures, 5days/wk x 10 wks)	no deaths	No signs of toxicity	Treon et al., 1943b
		309	6	" "	no deaths	Very slight conjunctival congestion	
		773	6	" "	no deaths	Slight conjunctival congestion and salivation	
		1414	6		no deaths	Slight lethargy Conjunctival congestion and irritation	
		3082	6	21 (15 exposures, 5days/wk x 3 wks)	2/4 died	Light narcosis, labored breathing, incoordination, salivation, conjunctival congestion and irritation	
	Monkey, rhesus, 1 animal	608	6	70 (50 exposures, 5days/wk x 10 wks)	no deaths	Slight conjunctival congestion (see text)	
Methylcyclohexanone	Rabbits, young, 4 per exposure group	182	6	70 (50 exposures, 5days/wk x 10 wks)	no deaths	No signs of toxicity	Treon et al., 1943b
		514	6	" "	no deaths	Slight conjunctival congestion	
		1139	6	21 (15 exposures, 5days/wk x 10 wks)	no deaths	Lethargy, slight salivation and lacrimation, conjunctival congestion	
		1822	6	" "	no deaths	Lethargy, salivation, lacrimation, conjunctival congestion and irritation	

Table 94., (cont'd)

Chemical	Animal	Conc. (ppm, v/v)	Hr/ Day	Duration Days	Mortality	Details	Reference
Isophorone	Rats, male, Wistar, 90-120 g	25	8	42 (30 exposures, 5days/wk x 6 wks)	no deaths	No apparent signs of toxicity	Smyth et al., 1942 and Smyth, 1941b
		50	"	" "	no deaths	Evidence of lung and kidney pathology	
		100	"	" "	2/10 died	Evidence of lung, spleen, and kidney pathology	
		200	"	" "	1/9 died	" "	
		500	"	" "	5/10 died	" " Nose and eye irritation	
	Guinea pigs, both sexes, 250-300 g	25	8	42 (30 exposures, 5days/wk x 6 wks)	no deaths	No apparent signs of toxicity	
		100		" "	no deaths	Evidence of lung and kidney pathology	
		200	8	" "	2/9 died	Evidence of lung and kidney pathology	
		500	8	" "	4/10 died	Evidence of lung, kidney, and liver pathology	
Acetophenone	Rats, male, 60-70 g, 15 per exposure group	.143 (0.007 mg/m^3)	24	70	no deaths	No apparent signs of toxicity	Imasheva, 1966
		1.43 (0.07 mg/m^3	24	70	no deaths	Variable changes in cholinesterase activity, decrease in alblumin to α-globulin ratio, and dystrophy of liver	

seem to be the primary responses. However, in chronic exposures (15 ppm x 7 hrs/day x up to 100 exposures), lung irritation is apparently not severe, but slight kidney injury is indicated by increased organ weight and pathological changes in the kidney tubules (Dow Chemical, unpublished data).

Smyth and coworkers (1942) compared the subacute inhalation toxicity of mesityl oxide and isophorone. Pathological details of these studies are given by Smyth (1941 b and c). Unlike acute exposures in which mesityl oxide is more toxic, isophorone caused greater pathological damage and mortality in comparable subacute exposures. Death from isophorone exposure was due primarily to kidney and lung damage. Lungs showed congestion and hemorrhage typical of ketone exposure. Kidney pathology included congestion, cloudy swelling, degeneration, and necrosis of the epithelial vessels of the renal tubules. Mesityl oxide, however, caused much less severe lung irritation and cloudy swelling of the kidneys. Lethality patterns were also quite different for these two ketones. Mesityl oxide caused no deaths in multiple exposures under 500 ppm. This may indicate that mesityl oxide caused death by accumulating to anesthetic concentrations with repeated exposure. Isophorone, however, causes a gradual decrease in mortality in multiple exposures to decreasing concentrations. This pattern is indicative of cumulative toxic effects (Smyth _et_ _al_., 1942).

Comparable details are not available in the remaining studies summarized in Table 94 . Some liver damage seems apparent in rats after 70 day continuous exposure to 1.43 ppm acetophenone but no kidney pathology was noted. Cholinesterase activity was observed in 5 of the 15 rats in each group and changes were observed, though not consistent ones; in three rats the cholinesterase activity decreased 22% and in one rat the activity increased by 45%. Total blood protein and albumin levels were also measured in 5 rats of each group. It was found that in the 1.43 ppm group, there was a distinct decrease in albumin/globulin ratio even though the total protein stayed the same (Imasheva, 1966).

In multiple exposures to cyclohexanone and methylcyclohexanone, Treon and coworkers (1943b) noted effects in rabbits typical of acute inhalation toxicity. Even though narcosis was unusually protracted in acute exposures to guinea pigs (Specht _et_ _al_., 1940), no obvious cumulative effects were noted in these repeated exposures to rabbits. In the one monkey exposed to cyclohexanone (608 ppm x 6 hrs/day x 50 exposures), severe injuries of the lungs, liver, kidneys, and heart muscle were associated with a chronic pulmonary infection (Treon _et_ _al_., 1943b).

Recently, Tison and coworkers (1976) have found that rats and chickens exposed to 650 ppm methyl _n_-amyl ketone continuously for 1000 hours failed to develop a peripheral neuropathy.

3. Peripheral Neuropathy

The recent outbreak of cases of peripheral neuropathy in workers occupationally exposed to methyl _n_-butyl ketone (see Section III-C, p. 192) has led to long-term experimental exposures of rats, cats, dogs and chickens. The clinical and histological evidence indicates that methyl _n_-butyl ketone (MBK) and 2,5-hexanedione, a metabolite of MBK (see Section III-B, p. 174), both produce a peripheral neuropathy known as "dying-back" disease (Spencer and Schaumburg, 1974b). Although the mechanism of action of these ketones has not been determined, several theories on the action of other chemicals causing this neuropathy have been published; a detailed discussion of these is presented by Spencer and Schaumburg (1974a, [illegible]).

Many of the studies published on MBK-induced neuropathy involve inhalation exposure. The results of these are presented in Table 95.

Duckett and his associates (1974a, b) have found both clinical and histological signs of neuropathy in nine rats exposed to 200 ppm (by volume) MBK for eight hours a day, five days a week, for six weeks. The rats experienced muscular weakness in all limbs lasting a few hours after each experimental period. After the six weeks exposure, the rats were killed and their sciatic nerves examined histologically. The examination revealed axonal swelling, beading, and degeneration as seen in secondary myelin breakdown.

In addition to this study, Duckett and coworkers (1974a, b) exposed eight rats to a mixture of 200 ppm MBK and 2000 ppm methyl ethyl ketone (MEK) for the same time periods. Three of the rats died; the cause of death was not reported. Results of this combined exposure were similar to those after exposure to 200 ppm MBK. However, these rats required a full day, rather than a few hours, to recover from one exposure period (Duckett _et_ _al_., 1974b).

Recently, Saida and coworkers (1976) exposed three dozen rats, each weighing 160-180 g, continuously to either MBK at 225 ppm, MEK at 1125 ppm or the combination of MBK:MEK at 225:1125 ppm. On the basis of clinical findings of "paralysis," no neuropathy was detected in the animals exposed to MBK alone or to MEK alone after 55 days in each case, but neuropathy was found after 25 days in animals exposed to a mixture of these compounds. They suggested that there is a marked potentiation of peripheral neurotoxicity when animals are exposed to a combination of methyl ethyl ketone and methyl butyl ketone in a ratio of 1 to 5. Saida _et_ _al_. (1976) also exposed another group of rats to MBK at a level of 400 ppm continuously 24 hours per day. These animals developed clinical evidence of neuropathy after 42 days, but pathological evidence of

Table 95. Inhalation Studies on Methyl *n*-butyl Ketone Induced Peripheral Neuropathy

Laboratory Animals	Number Exposed, Strain Sex, Age, Weight	Dosage Schedule	Dosage Levels	Psychological Effects	Reference
Rats	9, NS	Eight hours/day Five days/week	200 ppm	Clinical and histological signs of peripheral neuropathy	Duckett *et al.*, 1974a, b
	8, NS		200 ppm plus 2000 ppm methyl ethyl ketone	Clinical and histological signs of peripheral neuropathy; role of MEK not yet determined	Duckett *et al.*, 1974a, b
Rats	4, Sprague-Dawley	Twenty-four hours/day, Seven days/week, for sixty days	Initial-600 ppm Final-400 ppm	First clinical signs of peripheral neuropathy in sixty days; concurrent histological signs	Mendell, 1974 Mendell *et al.*, 1974
Rats	NS	Six hours/day Five days/week for five months	100 ppm 300 ppm	No clinical signs of peripheral neuropathy	Raleigh *et al.*, 1975
Rats	6, young adults 3, control	Six hours/day Five days/week up to four months	1300 ppm	Clinical signs of peripheral neuropathy in three to four months, concurrent histological signs	McDonough, 1974 Spencer *et al.*, 1975
Cats	4, domestic	Twenty-four hours/day, Seven days/week, for sixty days	Initial-600 ppm Final-400 ppm	First clinical signs of neuropathy in thirty-three days; concurrent histological signs	Mendell, 1974 Mendell *et al.*, 1974
Cats	NS	Six hours/day Five days/week for five months	100 ppm 330 ppm	No clinical or histological signs of peripheral neuropathy No clinical signs and minimal histological signs of peripheral neuropathy	Raleigh *et al.*, 1975
Chickens	5, domestic	Twenty-four hours/day, Seven days/week, for sixty (+) days	Initial-200 ppm Final-100 ppm	First clinical signs of neuropathy in 35 days; concurrent histological signs	Mendell, 1974 Mendell *et al.*, 1974

neuropathy was present after only 28 days of exposure. Spencer and Schaumburg (1976a) exposed a colony of cats to a variety of ketones. Eighteen animals received twice daily subcutaneous injections containing 150 mg/kg of either undiluted commercial grade MIBK, MBK, MEK, a 9:1 mixture of MEK and MIBK respectively or a 9:1 mixture of MEK and MBK, 5 days a week for up to 8½ months. Four additional cats received twice daily injections of an equivalent volume of saline, 5 days a week for up to 5 months. It was noted that narcosis and excessive salivation commonly commenced shortly after injection. Abcess formation and skin ulceration were seen in several animals. Generalized weakness and death occurred in ten animals treated with MEK or MEK/MBK mixtures. Two animals treated with MBK alone died. MIBK was tolerated well. Neurological dysfunction was detected in cats intoxicated with MBK alone. Peripheral neuropathy developed after eight to ten weeks of intoxication and animals went on to display a severe hindlimb footdrop. By 16 weeks they were unable to walk and dragged themselves with weakened forelimbs. These animals displayed neuropathological evidence of dying-back disease in the central and peripheral nervous systems. Animals intoxicated with the 9:1 mixture of MEK and MBK displayed no clinical dysfunction but there was some pathological evidence of nerve damage. MEK produced no clinical or pathological evidence of neuropathy. MIBK or 9:1 mixtures of MEK and MIBK produced no clinical evidence of neuropathy.

A similarly designed experiment exposing rats to vapors of 100 ppm or 330 ppm MBK for six hours a day, five days a week, for five months failed to reveal signs of neuropathy (Raleigh _et_ _al_., 1975). At the time of the preliminary report, Raleigh and coworkers (1975) had not completed the histological examinations. However, the findings of Duckett and his associates (1974a, b) would indicate that some clinical signs should have appeared in animals exposed to 330 ppm methyl n-butyl ketone over a five month period. Differences in sex and strain of animal as well as methodology (e.g., vapor penetrating system) may be responsible for some of this discrepancy; however, no details of these factors were given.

Experiments with rats exposed to higher concentrations of MBK have resulted in peripheral neuropathy. Coordinated studies by McDonough (1974) and Spencer and Schaumburg (1975a) reveal that exposure of six rats to 1300 ppm MBK for six hours a day, five days a week, for four months has led to peripheral neuropathy. In addition, six rats were exposed to commercial grade methyl isobutyl ketone (MIBK) at 1500 ppm for up to five months; three animals served as controls (Spencer et al., 1975) [Commercial grade MIBK is known to contain MBK as an impurity. Spencer and his associates (1973) had indicated that as much as three percent MBK was in the MIBK used in the experiment. Spencer (personal communication, 1975) reported that the actual percentage of MBK contamination was closer to 0.9 percent].

The MBK exposures led to slight narcosis by the fourth hour and some loss of coordination after five and one-half hours of exposure. The rats gained weight slowly, and beginning on the 73rd day of exposure, progressively lost weight. The animals suffered progressive weakness of both hind feet after three to four months of exposure, and the most severely impaired exhibited some forelimb weakness (Spencer and Schaumburg, 1975a; Spencer et al., 1975).

The histopathological findings reveal consistent patterns of abnormality in the central and peripheral systems after MBK exposure. Peripheral nerve degeneration was predominant in the intramuscular and distal portions of the nerve, with a secondary degeneration of the myelin sheath.

Abnormal axonal swellings located in the degenerating nerve fibers were comprised of masses of neurofilaments (Spencer and Schaumburg, 1975a; Spencer et al., 1975).

The rats exposed to 1500 ppm MIBK vapor showed only slight narcosis during the exposure period, normal weight gain, and no neurological signs after five months exposure (Spencer et al., 1975). Histological examination revealed only minor neurological changes with no apparent nerve fiber degeneration. Due to the small percentage of MBK in the commercial grade MIBK, further studies on the pure compound are being conducted to determine any possible neurotoxicity (Spencer, personal communication, 1975).

Further rat studies are reported by Mendell (1974) and Mendell and coworkers (1974). These studies were designed to approximate the period of occupational exposure in the Ohio case studies (see Section III-C-2, p. 193). Initially, four Sprague Dawley rats were exposed to 600 ppm MBK continuously for 60 or more days. This level was lowered during the experiment to alleviate some complications due to weight loss and lethargy. The rats began to show clinical weakness in 11 to 12 weeks. Pathology revealed swollen axons with increased numbers of neurofilaments and degeneration of the myelin sheath at the axonal swellings - results similar to those found by Spencer and coworkers (1975), cited above.

Additional studies involving the same continuous exposure schedule were conducted with chickens and cats (Mendell, 1974; Mendell et al., 1974). The chickens were initially exposed to 200 ppm MBK and the cats to 600 ppm; both of these levels also were cut to 100 and 400 ppm, respectively, in order to limit the range of toxic responses. The chickens showed clinical symptoms at 35 days; they were unable to stand upright. The cats were dragging their hind limbs beginning at weeks five through eight and later experienced forelimb weakness. Pathological findings were similar to those in the rats. Electromyograms (EMG) were conducted periodically on the cats and the first changes were noted after four to six weeks of exposure. The irregular EMG patterns were similar to those found in humans suffering from neuropathy (Mendell _et al._, 1974).

Cats exposed to either 100 ppm or 330 ppm MBK vapors for six hours a day, five days a week, for five months failed to show clinical signs of neuropathy (Raleigh _et al._, 1975). Only minimal histological changes were seen in the nervous tissue of the cats exposed at the 330 ppm level. Considering the different dosage schedules, the results of the cat exposures by Raleigh and associates (1975) and Mendell and coworkers (1974) are not necessarily incompatible.

A few studies conducted by subcutaneous injection of the ketonic solvents are reported for both methyl _n_-butyl ketone (MBK) and 2,5-hexanedione (see Table 96).

Raleigh and coworkers (1975) induced peripheral neuropathy in cats receiving subcutaneous injections of 150 mg/kg/day for five days a week over a two month period. Dogs, dosed on a similar schedule for two to four months, also showed symptoms of peripheral neuropathy. Experiments on guinea pigs given repeated topical applications of MBK did not produce clinical signs of neuropathy (Raleigh _et al._, 1975). Neither dosage level nor details on application methods were specified in this preliminary report.

In this same series of neuropathy studies, Raleigh and coworkers (1975) found signs of peripheral neuropathy in rats receiving 2,5-hexanedione subcutaneously or orally. The oral doses were administered as

Table 96. Subacute and Chronic Toxicity of MBK and 2,5-Hexanedione by Subcutaneous Injection

Ketone	Laboratory Animal	Dosage Schedule	Dosage Levels	Physiological Effects	Reference
2,5-hexanedione	Rats	Daily, five days/ week for 19 weeks	340 mg/kg/day	Development of peripheral neruopathy	Raleigh et al., 1975
	Rats, Six, Sprague-Dawley	Daily, five days/ week (a) for 13 weeks plus (b) for 6 to 10 weeks	0.1 ml 0.2 + 00.4 ml (230 to 340 mg/ kg/day	Clinical signs of dysfunction: pathological signs of peripheral neuropathy	Spencer and Schaumburg 1975b,c
Methyl n-butyl ketone (MBK)	Cats	2x daily, five days/ week, 2-4 months	300 mg/kg/day total	Produced peripheral neuropathy	Raleigh et al., 1975
	Dogs	2x daily, five days/ week, 2-4 months	300 mg/kg/day total	Produced peripheral neuropathy	" "

25 ml of a 0.5 percent solution of 2,5-hexanedione, or 520 mg/kg/day for approximately two months. The subcutaneous injections were given at a rate of 340 mg/kg/day, five days per week for 19 weeks.

Detailed reports on the subcutaneous injection of 2,5-hexanedione in six 400 gram Sprague-Dawley rats are presented by Spencer and Schaumburg (1975b, c). These rats were injected with 0.1 ml of the dione five days a week for 13 weeks plus 0.2 ml or 0.4 ml (~ 230 or 340 mg/kg/day) for six weeks. A symmetrical weakness of hind limbs and feet, characterized by a waddling gait, occurred in some animals. The rats were examined weekly and sacrificed on or before the appearance of clinical signs. All animals exhibited pathological changes indicative of "dying-back" disease regardless of the presence of clinical symptoms.

Nerve fiber degeneration was most apparent at the distal portions of nerves with proximal nerve fiber presentation. Abnormalities included axonal swellings which were comprised of masses of neurofilaments as well as areas of demyelination. Additional pathological findings were similar to those seen in animals exposed to methyl n-butyl ketone (Spencer and Schaumburg 1975b, c). Spencer and Schaumburg (1976b) studied the clinical and neuropathologic effects on rats (six in each group) of drinking 0.5% solutions of various ketones administered for three months. These compounds included 2,5-hexanedione, 2,5-hexanediol, 2,4-hexanedione, 2,3-hexanediol, 1,6-hexanedione and 3,5-heptanedione. 2,4-Hexanedione was administered for one month and the animals were only examined clinically. Weight loss and clinical peripheral neuropathy developed in rats drinking 2,5-hexanedione, 2,5-hexanediol. Neuropathological changes were found in vulnerable areas of the central and peripheral nervous systems. No abnormalities were found in the other experimental animals.

4. Sensitization, Repeated Doses

No sensitizing effects have been reported in the ketones. As indicated in Section III-C-3-d (p. 203), skin sensitization tests for ethyl n-amyl ketone and acetophenone were carried out on human volunteers; the ketones produced no sensitization (Kligman, 1971 and 1972).

5. Teratogenicity

Little work has been done on the teratology or embryotoxicity of ketonic solvents. Griggs and coworkers (1971) and Weller and Griggs (1973) have reported on the effect of cyclohexanone vapors on chick embryos. One other ketone, methyl ethyl ketone (MEK) has been studied for effects on rat embryos and fetuses (Schweta et al., 1974).

Griggs and his associates (1971) exposed groups of eggs to unspecified concentrations of cyclohexanone vapors for three or six hours prior to incubation. Other groups were incubated for 96 hours at 37°C before exposures of three, six, or twelve hours. After 13 days, the embryos were examined for abnormalities. Examinations revealed normal head, beak, toes, eyes, feathers, and extra-embryonic membranes. Macroscopically, hearts and brains were normal. Livers from the experimental group were darker than the controls. The groups exposed prior to incubation weighed significantly less than their controls. The embryos exposed for three hours post incubation differed significantly in both weight and percent mortality.

Some of the chick embryos in all groups were allowed to hatch. Those exposed for three or six hours pre-incubation and six or twelve hours post-incubation were normal in appearance and behavior, although the percent mortality for these groups was 20 to 50 percent, as compared to 10-20 percent for controls.

The chicks from both groups exposed three hours post-incubation were unable to walk properly or maintain posture. Their only apparent physical abnormality was inwardly curled toes. Weller and Griggs (1973), discussing the same studies, indicate that the chicks appeared normal at birth and developed locomotor difficulties within a few hours. Both Griggs and coworkers (1971) and Weller and Griggs (1973) indicate that cyclohexanone has a functional, rather than morphological, teratogenic effect which may be due to an upper motor neuron lesion. Weller and Griggs (1973) suggest that the lesion might be localized at the neuromuscular junction. These investigators indicate further studies utilizing mammalian embryos are in progress.

Experiments conducted by Schwetz and his coworkers (1974) involved exposing adult female Sprague-Dawley (Spartan) rats to methyl ethyl ketone (MEK) at nominal concentrations of 1000 ppm and 3000 ppm. Pregnant rats were exposed for seven hours per day on days 6 through 15 of the gestation period. None of the litters were totally resorbed, and the resorbtion rate was not altered by exposure to MEK. Fetal body measurements in the 1000 ppm group were decreased somewhat, though no such change was seen in the 3000 ppm group. Although no significant increase in specific gross, soft tissue, or skeletal anomalies was found at 1000 ppm, a significant increase in exposed litters having fetuses with skeletal abnormalities was found. At 3000 ppm, a significant proportion of the litters had fetuses with gross external anomalies or internal soft tissue anomalies (see Table 97). Exposure to either level of methyl ethyl ketone had no apparent effect on the mother rats.

Table 97. Effect of Inhaled MEK on the Incidence of Fetal Anomalies Among Rat Litters[a] (Schwetz *et al.*, 1974)

		Methyl ethyl ketone	
Solvent Concentration (ppm)	Control	1000	3000
Number of litters examined	43	23	21
% of litters affected (No. of litters)			
Gross	(0)	(0)	19 (4)[b,c]
Skeletal			
Skull anomalies (delayed ossification)	12 (5)	23 (5)	(0)
Lumbar ribs or spurs	24 (10)	27 (6)	38 (8)
Vertebral anomalies (bipartite centra)	21 (9)	18 (4)	33 (7)
Sternebral anomalies (bipartite; delayed ossification	(a) 61 (14) (b) 11 (2)	65 (15)	43 (9)[b]
Total skeletal	58 (25)	95 (21)[b]	81 (17)
Soft tissue			
Subcutaneous edema	33 (14)	9 (2)	48 (10)
Dilated ureters	12 (5)	30 (4)	24 (5)
Total soft tissue	51 (22)	70 (16)	76 (16)[b]

a Administered by inhalation seven hours a day on days 6-15 of gestation.

b Incidence significantly different from control by the Fisher Exact Probability test, $p < 0.05$

c Two brachygnathous and two acaudate fetuses.

* Data from the two control groups were combined for statistical comparison with the exposed animals in all categories except sternebral anomalies (delayed ossification)

Schwetz and his associates (1974) concluded that at 1000 and 3000 ppm exposure levels, MEK is embryotoxic, fetotoxic, and potentially teratogenic. No further studies by these workers on MEK teratogenicity are in progress (Schwetz, personal communication, 1975).

6. Mutagenicity

No information is available on the potential mutagenicity of the ketonic solvents in birds and mammals.

7. Carcinogenicity

Most of the ketonic solvents have not been tested for carcinogenicity. Methyl ethyl ketone applied twice weekly to the skin of mice at 50 mg per application caused no tumors over a one year exposure period (Horton et al., 1965).

Pathological examinations in chronic toxicity studies (see Section III-D-2, p. 252) also revealed no tumors.

8. Behavioral Effects

No behavioral effects of the ketonic solvents have been reported in birds and mammals. The effects on social insects are discussed in Section III-E-1 (p. 273) of this report.

9. Possible Synergisms

Little work on the possible synergisms of ketonic solvents has been reported. The joint toxic action of acetophenone and isophorone has been studied by Smyth and associates (1969b, 1970). In these experiments, each compound was tested with others in both equitoxic and equivolume mixtures.

When acetophenone is mixed with either tetrachloroethylene, formalin, or carbon tetrachloride on a 1:1 by volume basis, a more-than-additive degree of toxicity results. Isophorone was not found to have greater than a random "more-than-additive" or "less-than-additive" effect (Smyth et al., 1969b).

Smyth and coworkers (1970) utilized equitoxic mixtures in which the volumes of the two compounds were directly proportional to their respective rat oral LD_{50} values. The comparison of equivolume to equitoxic mixtures showed that the combination of isophorone and propylene oxide yielded a great difference in predicted-to-observed LD_{50}'s. The adjusted ratios were calculated as follows: where the predicted (P) to observed (O) ratio was greater than 1, the adjusted ratio was (P/O) -1; where the P/O <1, the adjusted ratio was 1- (O/P). In the above mentioned case, the equitoxic adjusted ratio was 0.16 and the equivolume adjusted ratio was -1.46. Acetophenone combinations were not as widely divergent (Smyth et al., 1970).

The synergistic effects of acetophenone combined with other compounds has been indicated by Ryazanov (1968). Ryazanov suggests a formula for calculating concentration effect levels as follows:

$$X = \frac{a}{m_1} + \frac{b}{m_2} + \frac{c}{m_3} \cdots$$

where: (1) X is the unknown total concentration

(2) a,b,c are substances whose concentrations are to be determined

(3) M_1, m_2, m_3 ... are their respective maximum permissible concentrations for isolated action.

The combination of acetophenone with any of the following - acetone, benzene, phenol - should not exceed an X value of 1.5 (Ryazanov, 1968).

10. Cataract Formation

Guinea pigs subcutaneously and topically administered cyclohexanone developed bilateral cataracts (Rengstorff et al., 1971). Rengstorff et al. (1971) report unpublished work by Callahan on 28 albino guinea pigs of both sexes from 9 to 18 weeks in age, weighing 385 to 650 grams. The solvent was dropped on a three-inch clipped dorsal surface of the guinea pig or injected subcutaneously for three times a week for three weeks. The animals were examined initially after 60 to 90 days and then every 30 days over a total of six months. The results of these studies are in Table 98. Cutaneous administration of (0.5 ml) caused bilateral cataracts in 25 percent of those dosed. Subcutaneously induced effects were not as prevalent.

Table 98. Cataracts Found in Guinea Pigs After Cutaneous and Subcutaneous Application of Cyclohexanone (Rengstorff *et al.*, 1971)

		Cataractous Responses **Cyclohexanone** Month				
Route	Animal	2	3	4	5	6
Cutaneous (0.5 ml)	1	o	o	o	o	X
	2	o	o	o	o	X
	3		o	o	x	x
	4-12	No effect				
				25%		
Subcutaneous 1:1 Solvent: Saline (0.05 ml)	1-4	No effect				
5% Solvent in saline (0.05 ml)	5		X	X	x	x
	6		o	o	o	x
	7-16	No effect				
				12%		

0 - Indicates no defect in lens.

x - Indicates isolated vacuolated area in periphery of lens.

X - Indicates extensive vacuolated areas involving the entire periphery of lens.

E. Toxicity - Lower Animals

1. Insect Alarm Pheromones

In recent years, certain naturally occurring ketones have been identified as insect alarm pheromones, chemicals capable of eliciting definitive distress reactions in certain social insects. Although the ketone pheromones are species specific for the type of response generated at a given concentration, the same ketone may serve as pheromone for several different species. In any given group, alarm behavior is induced only when the particular ketone or a very close stereochemical analogue is present in sufficient quantity (Amoore *et al.*, 1969). Table 99 lists some of the ketones commonly found as pheromones.

Table 99. Ketonic Solvents as Alarm Pheromones in Social Insects

Ketone/Alarm Pheromone	Insect	Reference
2-Heptanone (Methyl *n*-amyl ketone)	*Apis mellifera*	Shearer and Boch, 1965
	Atta sp.	Blum *et al.*, 1968
	Atta texana	Moser *et al.*, 1968
	Iridomyrmex pruinosus	Amoore *et al.*, 1969
	(Roger)	Blum *et al.*, 1963
Methyl heptenone	*Iridomyrmex* sp.	Cavill and Hinterberger, 1960
	Tapinoma sesile (say)	Wilson and Pavan, 1959
4-Methyl-2-hexanone	*Dolichoderus clark* (Wheeler)	Cavill and Hinterberger, 1962
4-Methyl-3-heptanone	*Atta* sp.	Blum *et al.*, 1968
	Atta texana	Moser *et al.*, 1968
	Pogomyrmex sp.	McGurk *et al.*, 1966
	Pogomyrmex badius	Blum *et al.*, 1971
6-Methyl-3-octanone	*Crematogaster* sp.	Crewe *et al.*, 1972
3-Octanone (Ethyl *n*-amyl ketone)	*Crematogaster* sp.	Crewe and Blum, 1970
	Myrmica brevinodis	Crewe and Blum, 1970
3-Nonanone (Ethyl *n*-hexyl ketone)	*Crematogaster* sp.	Crewe *et al.*, 1972
Propyl isobutyl ketone	*Tapinoma sesile* (say)	Wilson and Pavan, 1959

Blum and coworkers (1966) compared the activities of the 2-alkanones in releasing alarm behavior in *Iridomyrmex pruinosus*, an ant species that utilizes 2-heptanone (methyl *n*-amyl ketone) as an alarm pheromone. They tested ketones of varying carbon chain length for alarm releasing activity in this species of ant and rated them according to strength of alarm response (see Table 100, p. 275). Blum and coworkers (1966) found that the greatest alarm releasing activity occurred in the C_6 to C_9 ketones, especially the straight chain molecules structurally similar to 2-heptanone. Little or no activity occurred in response to exposure to the C_3 and C_4 compounds, which are highly volatile, or in the lighter molecular weight ketones ($C < 10$).

Table 100. The Activity of Ketones as Releasers of Alarm for *Iridomyrmex pruinosus* (Blum *et al.*, 1966)

Compound	Rating
2-Propanone	0
2-Butanone	0
2,3-Butadione	0
3-Buten-2-one	0
2-Pentanone	2
3-Pentanone	0
2,4-Pentadione	2
Methyl cyclopropyl ketone	1
3-Methyl-2-butanone	1
3-Methyl-3-buten-2-one	0
Cyclopentanone	0
2-Hexanone	3
2,5-Hexanedione	3
5-Hexen-2-one	3
4-Methyl-2-pentanone	1
4-Methyl-3-penten-2-one	1
4-Methyl-4-hydroxy-2-pentanone	1
3,3-Dimethyl-2-butanone	0
Cyclohexanone	0
2-Heptanone	5
3-Heptanone	4
4-Heptanone	4
4-Methyl-2-hexanone	2
5-Methyl-2-hexanone	2
5-Methyl-3-hexen-2-one	3
2,4-Dimethyl-3-pentanone	2
2-Octanone	4
3-Octanone	3
2,3-Octadione	2
2-Methyl-4-heptanone	3
5-Methyl-4-hepten-2-one	2
5-Methyl-5-hepten-2-one	2
6-Methyl-5-hepten-2-one	4
Acetophenone	2
Cyclooctanone	0
2-Nonanone	4
5-Nonanone	2
2,6-Dimethyl-4-heptanone	1
6,6-Dimethyl-3-heptanone	4
Phenyl ethyl ketone	2
Isophorone	0
2-Decanone	2
Phenyl *n*-propyl ketone	1
Cyclodecanone	0
2-Undecanone	0
2-Dodecanone	0
Phenyl *n*-amyl ketone	0
Cyclododecanone	0
2-Tridecanone	0

Similar pheromone activity ratings have been compiled for other insects - Pogomyrmex badius (Blum et al., 1971), the honey bee (Apis sp.) (Boch and Shearer, 1971), and the ant Atta texana (Moser et al., 1968). These studies reveal that the position of the carbonyl grouping on the chain, as well as the positioning of methyl group branching, affects the relative activities of the compound. If the carbonyl grouping is located centrally on the chain (Blum et al., 1966) or has branching groups nearby (Boch and Shearer, 1971), the relative activity is lessened.

Data in Table 101 indicate various stereochemical properties of compounds which influence their ability to act as surrogate alarm pheromones for Iridomyrmex pruinosus. The width and height as well as linear length of the molecule appear to be instrumental in determining the pheromone activity of the compounds. As seen in Table 101, n-butyl acetate, which most closely matches the insect's true pheromone, 2-heptanone, in these three areas, has a high activity rating (5). Two other compounds, 2-ethoxyethyl acetate and 2-octanone, both have width and height identical to those of 2-heptanone, though their lengths are somewhat longer. Both of these compounds have activity ratings of four. On the other hand, 2-hexanone, with a length less than that of 2-heptanone but identical in width and height, has even less activity - three. The chemical n-heptaldehyde, which is similar to 2-heptanone only in height, has the lowest activity rating.

Table 101. Physical Properties, Linear Dimensions, and Activity Ratings of Compounds Evaluated as Alarm Pheromones For I. pruinosus (Blum, 1969)

Compound	Molecular Weight	Boiling Point (°C) (at 760 mm Hg)	Linear Length A	Dimensions Width A	Height A	Activity[c] Rating
2-Hexanone	100	126	9.8	4.9	3.6	3
Cyclohexanone	98	156	7.1	6.1	4.7	1
2-Heptanone[a]	114	151	11.1	4.9	3.6	5
Cycloheptanone	112	178	7.3	6.6	5.0	1
n-Heptaldehyde	114	115	11.7	4.2	3.6	1
4-Methyl-2-hexanone	114	139	9.2	5.9	5.0	2
n-Butyl acetate	116	126	11.0	5.0	3.7	5
2-Ethoxyethyl acetate	132	156	12.3	4.9	3.6	4
2-Octanone	128	173	12.4	4.9	3.6	4
Cyclooctanone	126	200[b]	7.4	6.6	5.1	1

[a] Natural alarm substance

[b] 713 mm Hg

[c] A rating of one denotes least active and five most active

Amoore and associates (1969) have also found that little variation in structure is tolerated before the alarm activity decreases. The structural changes are correlated with activity ratings for 2-heptanone and several other compounds in Figure 41.

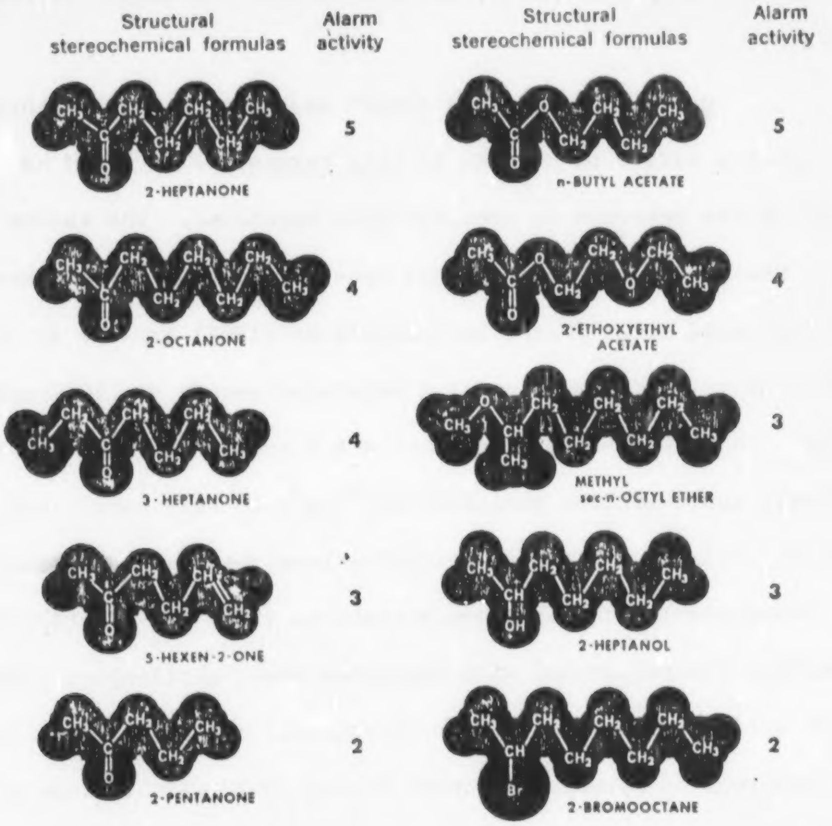
Structural stereochemical formulas
Alarm activity
Structural stereochemical formulas
Alarm activity
2-HEPTANONE
5
n-BUTYL ACETATE
5
2-OCTANONE
4
2-ETHOXYETHYL ACETATE
4
3-HEPTANONE
4
METHYL sec-n-OCTYL ETHER
3
5-HEXEN-2-ONE
3
2-HEPTANOL
3
2-PENTANONE
2
2-BROMOOCTANE
2

Figure 41A (left). Ketones. Many ketones related to 2-heptanone were tested for alarm-releasing activity on *Iridomyrmex pruinosus*. Nevertheless, only a rather limited amount of variation in molecular size and shape proved compatible with alarm activity.

Figure 41B (right). Nonketones. Provided that they bear a close resemblance to the molecular shape and polar location of 2-heptanone, a remarkable variety of unrelated chemicals were found to mimic its pheromone action. (Amoore *et al*., 1969)

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Further studies on alarm pheromones have been conducted to determine the concentration of ketones necessary to elicit the behavioral response. Wilson and associates (1969) have developed a mathematical model for determining the threshold concentrations of pheromone activity. This formulation depends on the emission rate of the compound, the diffusion coefficient of the compound in air, and the distance involved, as well as the time factor.

Moser and coworkers (1968) have determined the threshold concentrations of a series of ketones in Atta texana, an ant, and have shown that the nature of the response is concentration dependent. The ketone 4-methyl-3-heptanone, the alarm pheromone of this species, elicits alarm behavior at 10^{-5} cm^3 saturated air. [Moser and associates (1968) arrived at the ketone concentrations by serially diluting a saturated sample at 250°C and injecting the appropriate amount via syringe into a 6 ℓ container which housed the ants.] At the lowest concentration employed (10^{-6} cm^3, in this case), the worker ants detected the chemical; at higher concentrations they seemed attracted by the vapors. Considerably increased concentrations (10^{-5} for 4-methyl-3-heptanone) led to workers running around with mandibles open, challenging other workers. Peak alarm activity lasted for 45 to 75 seconds, and after about three minutes activity returned to normal. No other ketone could elicit alarm response at such a low concentration, but several, such as 2-heptanone, 3-heptanone, 3-octanone, 4-methyl-3-hexanone, and 5-methyl-3-heptanone, resulted in alarm at 10^{-2} cm^3 saturated air concentrations. Others caused little or no response or even attracted the worker ants (Moser et al., 1968).

The possibility of the alarm pheromones serving as toxicants in the social insects has been studied by Saslavasky and coworkers (1973) in the oriental hornet *Vespa orientalis* and by Quraishi and Thorsteinson (1965) in immature stages of *Aedes aegypti*. The latter investigators found that 1 μl/ml concentrations of 2-heptanone and 4-heptanone applied to the food supply of *A. aegypti* larvae and pupae caused a low degree of mortality (0-10%). Quraishi and Thorsteinson (1965) have also reported that 2-heptanone had a reversible anesthetic effect on the larvae, but not on the pupae, of the insect.

Several compounds, including the ketones 3-nonanone and cyclohexanone, were tested as alarm pheromones and toxins in the oriental hornet (Saslavasky *et al.*, 1973). Studies indicate considerable variation in response to the ketones by different age groups and types of colonies of hornets (see Table 102 below). As can be seen, the only commercially important solvent

Table 102. Response of Colonies and Groups of Imagines Towards Ketones (After Saslavasky *et al.*, 1973)

	Colony				Imagines			
	Queenright		Queenless		2-12 days old		12-30 days old	
Ketone	Alarm	Toxicity	Alarm	Toxicity	Alarm	Toxicity	Alarm	Toxicity
Cyclopentanone	0	A	0	A	0	C	0	C
Cyclohexanone	1	A	0	A	0	C	0	C
4-Octanone	2	B	2	A	0	E	0	D
3-Nonanone	4	B	0	A	0	E	2	C
2-Methyl-3-hexanone	3	A	2	A	0	D	2	D
6-Methyl-5-hepten-2-one	4	A	4	A	2	A	2	A
2-Methyl-3-nonanone	0	A	2	A	0	A	0	A

Alarm behaviors are expressed as follows:

0 = nonresponse, 1 = weak response, 2 = reasonable response, 3 = strong response, 4 = very strong response

Mortality is expressed as follows:

A = 0 percent, B = 25 percent, C = 25-50 percent, D = 50-75 percent, E = 75-100 percent

Spreading and feeding with ketones caused convulsion and death (0.5-5 minutes) tested here, cyclohexanone, does not elicit much alarm behavior, although it does cause some mortality in the younger groups of imagines - a combination of workers, males and young queens. Saslavasky and coworkers (1973) also note that the larvae and pupae of the hornet are subject to higher mortality from exposure to the ketones as are the same developmental stages in the yellow-fever mosquito _A. aegypti_ (Quraishi and Thorsteinson, 1965).

2. Other Toxic Effects

The 96 hour LD_{50} of methyl ethyl ketone to mosquito fish (_Gambusia affinia_) is given as 5.6 g/ℓ (Wallen _et al._, 1957). Buzzell and coworkers (1968) report that a 96 hour exposure to 10 g/ℓ of this ketone results in no mortality to bluegill fingerlings (_Lepomis macrochirus_).

Crisp and coworkers (1967) have demonstrated that four ketones - acetone, methyl ethyl ketone, diethyl ketone, and cyclohexanone - induce narcosis in barnacle larvae. In this study, thermodynamic activities rather than concentrations are used in describing the exposure conditions. The threshold narcotic response is defined as loss of forward movement while the appendages of the larvae are still active. The results for the four ketones are summarized in Table 103.

Table 103. Thermodynamic Activities of Various Ketones Producing Threshold Narcosis in the Nauplius Larvae of the Barnacle, _Elminius modestus_ (Crisp _et al._, 1967)

Ketone	Average Thermodynamic Activity
Acetone †	1.9×10^{-2}
Methyl ethyl ketone	2.0×10^{-2}
Diethyl ketone	3.55×10^{-2}
Cyclohexanone	2.05×10^{-2}

† = _Balanus balanoides_ larvae used

A pattern of decreasing potency - indicated by increasing thermodynamic activity - with increasing chain length was noted not only for the acyclic ketones summarized in Table 103, but also for homologous series of aliphatic hydrocarbons, halogenated hydrocarbons, alcohols nitriles, and ethers.

F. Toxicity - Plants

No studies have been encountered concerning the effects of any of the ketonic solvents on plants.

G. Toxicity - Microorganisms

As discussed previously (see p. 128), certain microorganisms have been shown to degrade various ketonic solvents. Relatively little, however, is known about the toxic effects of ketones on microorganisms. Using a mixed microbial culture, Buzzell and coworkers (1968) state that the mean tolerance levels for methyl ethyl ketone and acetone are 14 g/ℓ and 24 g/ℓ, respectively. As indicated in Figure 42, Egyud (1967) has shown that a variety of ketones, including many ketonic solvents, have only a mild and apparently transient inhibitory effect on the growth of Escherichia coli at ketone concentrations of 1 x 10^{-3}M. Only methyl vinyl ketone has any pronounced inhibitory effect. Mesityl oxide, a structurally related unsaturated ketone of some commercial importance, is no more toxic than most of the saturated ketones.

Some of the ketonic solvents have been shown to have mild to marked stimulatory effects on the germination rate of uredospores of Puccinia gaminis, a fungus which causes stem rust in wheat (French, 1961). This has been demonstrated by placing dilutions of various ketones in the annulus of a Conway diffusion cell and floating uredospores on a phosphate buffer in the inner compartment. After incubation at 16°C for ninety minutes, the extent of germination was determined. The degree of germination was then compared to a standard stimulator and relative activity ratings assigned (see Table 104).

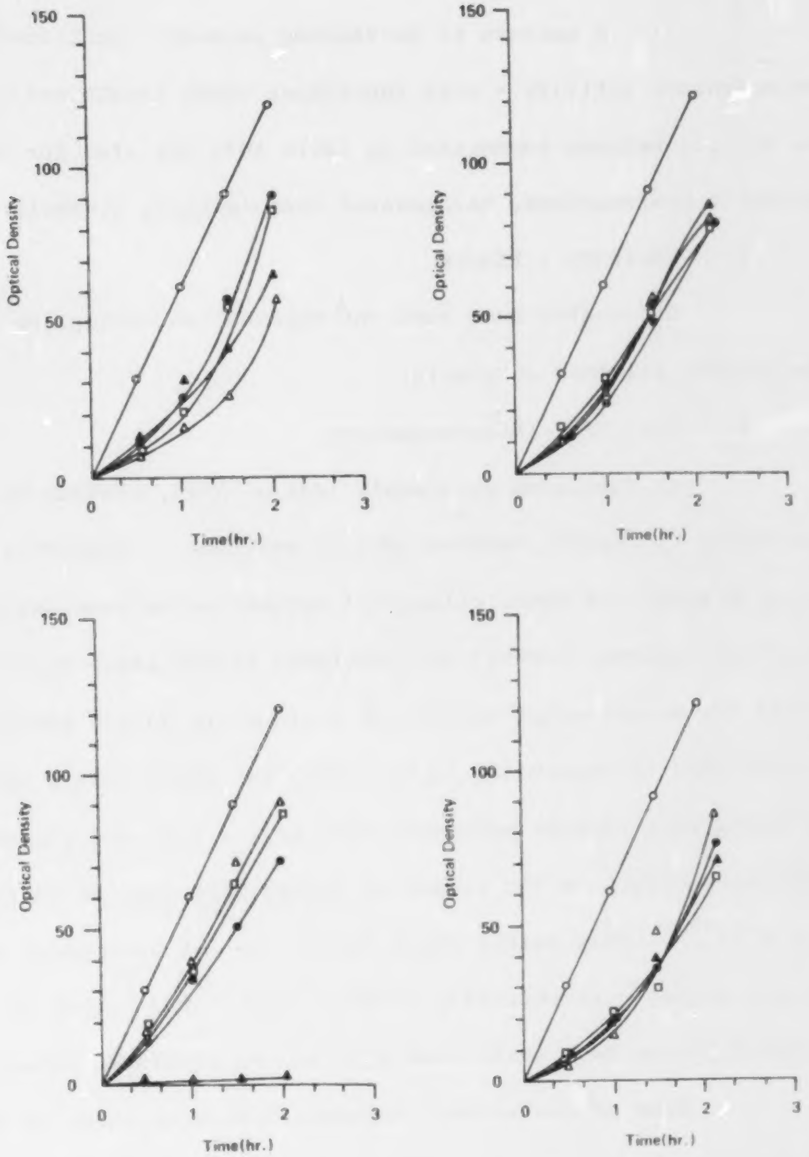

Figure 42. The Effect of Ketones on the Proliferation of *E. coli*. - The assay contained 0.25 ml of bacterial suspension, 4.0 ml of M-9-glucose media, 0.5 ml of the inhibitor (1 x 10^{-2}M) and water to bring up the final volume to 5.0 ml. In the control, the inhibitor was replaced with water. The final concentration of the inhibitor was 1 x 10^{-3}M. The amount of bacterium was 2.8 x 10^{8} cells/ml. The reaction mixture was incubated at 37°C under aerobic conditions.

(a) ○——○ control, △——△ acetone, □—□ methyl-ethyl ketone, ●——● 2-pentanone, ▲——▲ 2-hexanone.
(b) ○——○ control, △——△ 2-octanone, □—□ 2-nonanone, ●——● 2-decanone, ▲——▲ 2-undecanone.
(c) ○——○ control, △——△ 2-dodecanone, □—□ 2-tridecanone, ●——● methyl-isobutyl ketone, ▲——▲ methyl-vinyl ketone.
(d) ○——○ control, △——△ mesityl oxide, □—□ acetophenone, ●——● 2-acetylfuran, ▲——▲ cyclopropyl-methyl ketone.

(Egyud, 1967)

Table 104. Stimulatory Activity of Some Ketones on Uredospore Germination (French, 1961)

Ketone	Dilution	Rating*
Methyl ethyl ketone	10^{-3}	27
Methyl *n*-propyl ketone	10^{-3}	88
Methyl isopropyl ketone	10^{-3}	103
Diethyl ketone	10^{-3}	93
Methyl *n*-butyl ketone	10^{-3}	87
Methyl *n*-amyl ketone	10^{-4}	105
Dipropyl ketone	10^{-4}	100
Methyl *n*-hexyl ketone	10^{-6}	150
Mesityl oxide	10^{-3}	69

* Rating: >80 = highly stimulatory; 20-80 = stimulatory; 0-20 = inactive

In comparing these results with a variety of other ketones, aldehydes, alcohols, and hydrocarbons, French (1961) has concluded that this stimulatory effect is non-specific in terms of chemical reactivity, and probably attributable to the ketones (or other compounds) serving as substrates for enzyme systems in the fungal spores.

IV. Regulations and Standards

A. Current Regulations

1. Food, Drug, Pesticide Authorities

Several of the ketonic solvents are covered under food additive regulations and are regarded as safe food additives. Those included are methyl ethyl ketone, methyl n-propyl ketone, methyl n-amyl ketone, ethyl butyl ketone, dipropyl ketone, methyl isobutyl ketone, ethyl amyl ketone, methyl hexyl ketone, methyl heptyl ketone, methyl nonyl ketone, acetophenone, and benzophenone (FDC Law Reporter, 1975).

2. Air and Water Acts

Rule 66 of the Los Angeles Air Pollution Control District limits the industrial emission of solvents. When an organic solvent is exposed to baking, heat-curing, heat-polymerizing, or flame contact, no more than 15 pounds per day may be emitted. When no baking, heat-polymerizing, or flame contact occurs, the emission of photochemically reactive solvents is limited to 40 lbs per day, but there is no limit imposed on non-photochemically reactive solvents. A photochemically reactive solvent is one which contains either: (1) 5% or more by volume of olefinic compounds; (2) 8% or more by volume of aromatic compounds with 8 or more carbon atoms, except ethyl benzene; (3) 20% or more of ethyl benzene, branched ketones, trichloroethylene, or toluene; or (4) a total of 20% or more of a mixture or blend from the preceding classes of compounds. Whenever a compound has a structure which meets the specification of more than one class, it is always assigned to the class with the least allowable percentage (Feldstein, 1974).

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Rule 66.1 extends the control over emissions to architectural coatings and Rule 66.2 to disposal of solvent wastes (Feldstein, 1974). Rule 66C limits total organic emissions (photochemically reactive and non-photochemically reactive) to 3000 lb/day or 450 lbs in any one hour (Feldstein, 1974).

Regulation 3 of the San Francisco Bay Area Air Pollution Control District differs from Rule 66. The most important difference in terms of the regulations of the ketonic emissions is that the branched chain ketones are exempted. However, isophorone and mesityl oxide (as olefins) and acetophenone (as a substituted aromatic) are designated as reactive. The basic requirement of Regulation 3 is to limit emissions of organic compounds to less than 50 ppm. If over 50 ppm are emitted, the operation is not in violation, provided one of the following conditions can be met:

1. A complying material is being used (no reactive organic compounds and no heat applied.
2. There are less than 5% reactives in the emission.
3. There are less than 10 lbs/day reactive organic compounds in the emission or less than 20 lbs/day total organic compounds in the emission.
4. The reactive compounds have been reduced by 85% overall.

3. Other EPA Authority - None

4. OSHA

The Occupational Safety and Health Administration (OSHA) has listed permissible levels in workroom air for several of the ketonic solvents. Those included are listed in Table 105.

On May 8, 1975, OSHA released proposed standards for six of the ketonic solvents (OSHA, 1975d). These proposed regulations for methyl ethyl ketone, methyl _n_-propyl ketone, methyl isobutyl ketone, methyl _n_-amyl ketone, ethyl n-butyl ketone, and cyclohexanone cover the permissible workroom air concentrations (see Table 105), respiratory protection devices, and hazardous location classifications as well as fire hazard and type of liquid classifications. Cyclohexanone is classified as a combustible liquid; the others would be considered as flammable liquids (OSHA, 1975c). Initially, public hearings were set for August 5 with June 20, 1975, as the deadline for interested persons to submit written data, views and arguments. However, due to many requests for extension of the comment period, a new deadline was set for July 21, with hearings set back to September 3, 1975 (OSHA, 1975a). Some of the controversy is centering on the permissible levels in workroom air. The proposed regulations establish certain mandatory procedures for the employer, should any employee be exposed to one half the airborne concentrations based on a time-weighted average. On August 29, 1975, OSHA (1975b) issued a request for comments on the inflationary impact of the proposed standards; such information will be considered after the oral testimony is heard in September. Inflationary impact statements will be prepared and further hearings will be held after their release (OSHA, 1975b).

Table 105. OSHA Standards For Ketones in Workroom Air (OSHA, 1974)

Ketone	ppm[a]	ppm[b]
Saturated aliphatics		
Methyl ethyl ketone	200	590
Methyl n-propyl ketone	200	700
Methyl n-butyl ketone	100	410
Methyl isobutyl ketone	100	410
Methyl n-amyl ketone	100	465
Ethyl n-butyl ketone	50	230
Diisobutyl ketone	50	290
Other Saturated		
Diacetone alcohol	50	240
Unsaturated aliphatics		
Mesityl oxide	25	100
Alicyclic and Aliphatic		
Cyclohexanone	50	200
Isophorone	25	140

a. Parts of vapor or gas per million parts of contaminated air by volume at 25° C and 760 mm Hg pressure.

b. Approximate milligrams of particulate per cubic meter of air.

5. DOT

Transportation of classified liquids is controlled by ICC regulations which have been described in Section II-D-2, p. 104.

6. Other Federal

None

7. States, Counties

None

8. Foreign Countries

Foreign countries have adopted food regulations and permissible workroom air levels for some of the ketones. The Council of Europe (1970) lists ethyl n-amyl ketone as a temporarily admissible artificial flavoring substance; it has also listed acetophenone with an admissible daily intake of 1 mg/kg. Permissible workroom levels in other countries for three of the solvents are given in Table 106.

Table 106. Permissible Workroom Air Levels of Ketonic Solvents: Foreign Countries (Winell, 1975)

Ketone	USA OSHA[a] 1974 mg/m^3	BRD[b] 1974 mg/m^3	DDR[c] 1973 mg/m^3	Sweden 1975 mg/m^3	USSR 1972 mg/m^3
Methyl ethyl ketone	590	590	300	440	200
Methyl n-propyl ketone	700	700	---	---	200
Cyclohexanone	200	200	---	---	10

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[a] OSHA - Occupational Safety and Health Administration

[b] BRD - Federal Republic of Germany

[c] DDR - German Democratic Republic

B. Consensus and Similar Standards

1. TLV

Threshold Limit Values (TLV's) have been published for several of the ketones (see Table 107).

Two ketone TLV's have been changed in the 1974 listing prepared by the American Conference of Governmental Industrial Hygienists (ACGIH). That for diisobutyl ketone was lowered from a 50 ppm limit to a 25 ppm value upon reevaluation of data presented by Silverman and coworkers (1946), in which these workers found some eye irritation at 50 ppm exposure. The TLV for isophorone was lowered from 10 ppm to 5 ppm due to a June, 1973, communication to the TLV committee regarding fatigue and general illness in workers exposed to levels of 5 to 8 ppm isophorone (Ware, 1973).

2. Public Exposure Limits

None

Table 107. Threshold Limit Values For Workroom Conditions For 1974

Ketone	ppm	mg/m3
Simple Saturated		
Methyl ethyl ketone	200	590
Methyl _n_-propyl ketone	200	700
Methyl _n_-butyl ketone	100	410
Methyl isobutyl ketone	100	410
Methyl _n_-amyl ketone	100	465
Methyl isoamyl ketone	100	475
Ethyl _n_-butyl ketone	50	230
Diisobutyl ketone*	25	150
Other Saturated		
Diacetone alcohol	50	240
Unsaturated		
Mesityl oxide	25	100
Alicyclic and Aliphatic		
Cyclohexanone	50	200
Isophorone*	5	25

*1974 Revision

Summary and Conclusions

This study examines the potential environmental impact of ketonic solvents with the exception of acetone. Most of the selected ketones fit into two major classifications: (1) straight-chain ketones, including methyl ethyl ketone (MEK), cyclohexanone, diethyl ketone, methyl n-propyl ketone, methyl n-butyl ketone, ethyl n-butyl ketone, 2,5-hexanedione (acetonylacetone), and 2,4-pentanedione (acetylacetone), and (2) branched-chain ketones which are manufactured from acetone, including methyl isobutyl ketone (MIBK), mesityl oxide, diacetone alcohol, trimethylnonanone, and diisobutyl ketone. These categories dominate both ketone production and consumption in solvent formulations. Acetophenone is the most important of the remaining ketones. Others which were considered include diisopropyl ketone, methylcyclohexanone, and benzophenone.

Annual production for the selected ketones in 1973 was estimated at approximately 1.5 billion pounds. Most of the production was consumed in industry either as a solvent or as a chemical intermediate; a relatively small proportion of the ketones are formulated into consumer products. Relatively few ketones dominate the market. The three major ketones in order of decreasing production importance are cyclohexanone (638 million pounds), MEK (505 million pounds), and MIBK (155 million pounds). Some 95% of cyclohexanone is consumed in the production of adipic acid and ε-caprolactam for nylon manufacture. Most of the remainder (32 million pounds) is consumed as a solvent. MEK (ca. 400 million pounds) and MIBK (ca. 101 million pounds) are principally consumed in solvent blending. Other ketones (in order of importance as solvents) are diacetone alcohol, isophorone, mesityl oxide, and acetophenone. They are also chiefly consumed by industry. A large proportion of the aromatic ketones and high molecular weight, straight-chain ketones are used as flavor and fragrance additives or for intermediates in their production.

Ketonic solvents are consumed in greatest quantities in formulating coatings and allied products (such as inks and adhesives). Most of the solvents are consumed in industrial coatings (e.g., for automobiles, wood products, and metal products). This includes from 60 to 70% of total MEK and MIBK consumption. Less important solvent uses include lube oil dewaxing (about 5 to 10% of MEK); rare metal refining (branched chain ketones including about 5 to 10% of MIBK); pesticide formulations (including aerosol formulation); degreasers; paint, varnish, and rust removers; and solvents for other industrial processing.

The environmental release of the manufactured ketones primarily originates from the evaporation of solvent during drying of industrial coatings and allied industrial uses (e.g., inks and adhesives). Only a minor fraction of these evaporated ketones are recycled. The majority are either discharged to the atmosphere or disposed by other means (usually incineration). The release of evaporated ketonic solvents to the atmosphere is reduced to some extent as the result of complying with air pollution regulations, which are usually similar to Los Angeles Air Pollution Control District's Rule 66. It requires reduction of evaporated solvents prior to their release to the atmosphere, if they contain in excess of 20% of photochemically reactive (branched-chain) ketones and 5% of olefins (mesityl oxide and isophorone are olefins), and all solvents emitted from baking ovens.

Except when exposed to heat, straight-chain ketones are exempt from requirements to reduce emissions. Specific information on ketones discharged into the atmosphere was not available.

Other origins of atmospheric ketones include fugitive emissions from manufacture, transport, handling, and use. These losses do not appear to be as important as the losses from solvent evaporation. Losses in tank filling are estimated at 50 pounds of ketone lost per million gallons for each filling. Losses from storage are unknown, although it is known that some 40% of the ketone storage tanks do not control venting losses.

Some of the selected ketones occur naturally in food and are produced as an intermediate in biological oxidation of organic wastes. For example, the linear methyl ketones are intermediate products in the biological degradation of the corresponding alkanes. The straight chain ketones are commonly observed in foods in concentrations from the ppb to ppm level. As mentioned above, some ketones are added to food to improve flavor and fragrance.

The selected ketones are also produced by partial oxidation of aliphatic hydrocarbons. Automobile exhaust contains low concentrations of some ketones, including MEK, methyl _n_-propyl (and isopropyl) ketone, and mesityl oxide. Concentrations as high as 1.5 ppm have been observed. However, the average concentration is unknown. Automobile exhaust is not considered likely to be a major source of MEK, but could be important as a source of less heavily consumed commercial ketones such as methyl _n_-propyl ketone and mesityl oxide. Ketones could also be produced by atmospheric oxidation of hydrocarbons. It has been observed that olefins in the photochemical smog cycle will yield ketones, probably by ozonization.

Most of the selected ketones are chemically stable to the normal environmental conditions. With the exception of mesityl oxide, the ketones are stable to oxygen at ambient conditions; mesityl oxide forms a highly reactive peroxide. The ketones are biodegradable in soil and water. The lower chain length ketones appear to be the most susceptible. The introduction of chain branching, unsaturation, a second carbonyl group or cyclization appears to increase resistance to biodegradation. Atmospheric ketones degrade by photochemical processes. They are minor participants in photochemical smog production. Their contribution to smog production increases with the introduction of chain branching or unsaturation.

Ketones appear to migrate readily within the environment and readily move between the media (air, water, soil). The low molecular weight ketones are relatively water soluble and volatile. They are usually observed as components of surface waters and possibly originate from natural sources. There is little monitoring information available on the selected ketones in soil or air. From the physical properties, it is evident that ketones in soil as well as in water will volatilize, and atmospheric ketones will be washed out with rainfall. Ketones in the soil will probably migrate with surface and ground water.

In acute exposure, all of the ketonic solvents seem to act as physical toxicants causing narcosis with central nervous system depression. At sufficiently high doses, some selective renal toxicity may be induced. Although two of the ketones are neurotoxic, renal toxicity seems to be the most common effect of the majority of ketonic solvents during chronic exposures.

The most commercially significant ketonic solvents also seem to be the least toxic. Methyl ethyl ketone is reported to have no adverse effect on guinea pigs after inhalation exposures of 235 ppm x 7 hr/day x 60 exposures over 84 days. Similarily, hypobaric exposures to methyl isobutyl ketone at 100 ppm x 24 hr/day x 90 days had no effect on monkeys or dogs. Under the same exposure conditions, however, some kidney pathology has been noted in rats. Cyclohexanone is somewhat exceptional in that adverse chronic effects do not include kidney damage. In oral administration to rats for 180 days, 0.01 mg/kg/day had no effect and 0.05 mg/kg/day caused a slight decrease in stimulus response. Only at 5 mg/kg/day were degenerative morphological changes noted in the nervous system, liver, stomach and spleen. In inhalation, cyclohexanone seems to have a no effect level similar to methyl ethyl ketone: 190 ppm cyclohexanone x 6 hr/day x 50 exposures over 70 days caused no apparent adverse effects in rabbits.

Most of the remaining ketonic solvents cause chronic effects similar to methyl isobutyl ketone, but at markedly lower concentrations. Diacetone alcohol has been shown to cause cloudy swelling of the kidney tubules in rats on oral administration of 40 mg/kg/day x 30 days, but no effect at 10 mg/kg/day over the same period. Oral administration of acetophenone at 25 mg/kg/day x 30 days to rats caused slight increases in liver and kidney weights, but morphological damage was not demonstrated. In inhalation, acetophenone reportedly has no apparent toxic effect on exposures of .143 ppm x 24 hrs/day x 70 days. However, at 1.43 ppm, dystrophy of the liver and changes in blood protein fractions as well as plasma cholinesterase activity have been noted. The two most common unsaturated ketones, mesityl oxide and isophorone, seem to differ significantly in mode of action. Exposures of 500 ppm mesityl oxide x 8 hr/day x 10 exposures over 14 days caused death in rats and guinea pigs.

In that lower concentrations caused no adverse effects, death was attributed to the accumulation of mesityl oxide to anesthetic levels with consequent circulatory and respiratory depression as in acute exposures. Isophorone, at concentrations of 100 ppm - 500 ppm x 8 hr/day x 30 exposures or 42 days, caused fractional mortality in rats and guinea pigs roughly proportional to the concentration. Here, death was attributed to cumulative toxic damage of the kidneys and lungs. Over an exposure period of 8 hr/day x 5 days/week x 6 weeks, mesityl oxide and isophorone, at concentrations of 50 ppm and 25 ppm respectively, caused no apparent adverse effects.

Recently, considerable attention has been focused on the peripheral and central neuropathic properties of methyl n-butyl ketone and its metabolite 2,5-hexanedione. In chronic subcutaneous exposures, both of these compounds seem to have about the same neuropathic potency and should be regarded as occupational hazards. The ability of methyl n-butyl ketone to cause peripheral neuropathy in man during occupational exposure has been clearly documented in epidemiological surveys. The threshold level for chronic exposure to man is unknown. However, methyl n-butyl ketone exposures of 100 ppm x 6 hrs/day x 5 days/week x 5 months do not cause peripheral neuropathy in cats and rats. A lower limit to methyl n-butyl ketone induced neuropathy is further suggested by the presence of this ketone in milk and cream at levels of 0.007 - 0.011 ppm and 0.017 - 0.018 ppm, respectively. Nonetheless, neither of these neurotoxic ketones are normal constituents of human urine. The remaining ketonic solvents have not been shown to be neurotoxic on chronic exposures, although only commercial grades of methyl isobutyl ketone, containing a small amount of methyl n-butyl ketone, have been specifically screened and found not to produce unequivocal evidence of nerve fiber damage.

Little information is available on the teratogenic potential of ketones. Cyclohexanone has been shown to cause motor disturbances in new hatched chickens, but morphological teratisms have not been noted. The results of mammalian studies should be available in the near future. Methyl ethyl ketone at environmentally unrealistic concentrations (1,000 - 3,000 ppm) may be teratogenic to rats.

The carcinogenic or mutagenic potential of the ketonic solvents cannot be evaluated from the available data. On dermal exposure, methyl ethyl ketone did not cause carcinogenicity in mice when applied at 50 mg/mouse x twice weekly x 1 year.

Based on the available data, the potential for adverse effects from ketone exposure at reasonable environmental levels does not seem high. Both the neuropathic effects of methyl *n*-butyl ketone and the renal toxicity of the more common ketonic solvents seem to have threshold levels above environmental concentrations. However, the long term effects of these compounds have not been well characterized: most of the available information concerns exposures of under 180 days. In addition, other neurotoxic substances producing a rather similar pattern of nervous system disease (acrylamide, carbon disulphide, cresyl phosphates, metal salts) are also present in the environment in low levels. Further, information on mutagenicity, carcinogenicity, and teratogenicity is scant. Nevertheless, most of the ketonic solvents are normal constituents of food products and have been monitored in human urine. Because of the apparent inverse relationship between toxicity and commercial importance, the ranking of hazard potential among the various ketones has not been attempted. For instance, although MEK overwhelmingly dominates the ketonic solvent emissions, this compound appears to be among the least hazardous ketones. For the remaining ketones, the greater proportion of environmental contamination is probably not attributable to solvent use.

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